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DISSEMINATED LUPUS ERYTHEMATOSUS OCCURRING AMONG STUDENT NURSES*

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IN the course of a follow-up survey‡ on a group of 750 nurses who trained at a large municipal hospital between 1932 and 1946,[1] it was found that 3 of these girls had developed and succumbed to disseminated lupus erythematosus. These cases represent 23 per cent of the total mortality among the nurses, the disease being second only to tuberculosis as the major cause of death. The deaths in the entire group have numbered 13, and have been distributed as shown in Table 1.

The occurrence of lupus three times in this group is by itself a curious and unexpected finding, but its interpretation and significance are doubtful. These figures obviously cannot be compared to the causes of death in the general population of this age group and sex, since several artificial factors enter into the selection of this group to distort the pattern. A search for a factor common to the 3 cases, however, brought to light several circumstances that appear to have a direct bearing on the present-day concepts of the pathogenesis and etiology of the disease.

Etiology of Disseminated Lupus Erythematosus

Since the earliest reviews on the subject there has remained a group, mainly French, Austrian and Scandinavian, who consider the tubercle bacillus as the etiologic agent in lupus. The great volume of clinical and autopsy material, however, lends no support to this concept, and in this country at least it has been virtually discarded.[2]

A second group, consisting mainly of the British, have become convinced that the hemolytic streptococcus is most usually responsible for the disease. The evidence for this concept is reviewed below.

The etiology of lupus is less definitely stated in this country. Ginzler and Fox[3] (1940) state: "There is a tendency at present to regard the disease as a peculiar response, in a constitutionally predisposed person, to a variety of harmful agents." Multiple etiologic factors are in general considered to be instrumental. The varied etiologies postulated assume the form of tissue sensitization to and destruction by various bacteria or toxins, and are in agreement with Bloch's[4] dictum that "the type and course of the allergic reaction are independent of the nature of the antigen, but vary according in the localization of the antibody, that is, according to which organ reacts to the antigen." The streptococcus is again the organism most frequently incriminated, with the pneumococcus,[5] staphylococcus and even the gonococcus[6] receiving mention. Among nonbacterial agents, horse serum has received attention, as in the case of lupus described by Fox,[7] in which the disease followed the administration of prophylactic antitetanus serum. Throughout the entire pattern, hypersensitivity and allergy now receive major consideration.

Table 1. *Causes of Death Among 750 Nurses, 1932–1946.*

Cause of Death	No. of Cases	Percentage of Deaths
Tuberculosis	4	30.7
Disseminated lupus erythematosus	3	23.0
Staphylococcal septicemia	1	7.7
Carcinoma	1	7.7
Accident and suicide	2	15.4
War casualty	2	15.4

In spite of these various speculations the etiology of lupus has remained unknown. It is of interest, however, to review the accumulating evidence supporting the concept that includes lupus among other diseases thought to be associated with allergy and hypersensitivity.[3, 5–15]

Allergy or Hypersensitivity

The clinical and pathological features of the syndrome have been compared to the manifestations of serum sickness, and the correlation is frequently extremely suggestive. Indeed, lupus has been claimed by many to represent a prolonged, malignant form of serum sickness.[7]

The pathology of lupus has received critical consideration in several papers, and the findings are

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described as being entirely compatible with those of allergic or pathergic inflammation.[5, 6, 10, 12, 15] In particular, the work of Rich,[15] which has recently come to include lupus, lends support to this concept. According to Klemperer et al.,[10] the common denominator of the pathology of the disease is the widespread fibrinoid degeneration of collagen, considered also to be the pathology of hypersensitivity and hyperergic inflammation, as in the Arthus phenomenon. The fatal outcome in the disease has been attributed to the pronounced necrotic components of these allergic processes,[6] localized in the experimental Arthus phenomenon but widespread in lupus.

Impressive also is the pathological finding in the kidneys of horses rendered hyperimmune to bacteria for the purpose of developing therapeutic antitoxin, on which typical wire-loop glomerular lesions were found.[5, 11] These lesions, described by Klemperer et al.[8] as being a characteristic finding in lupus, have been found in only three situations: in disseminated lupus, in eclampsia of pregnancy in the human being and in horses in which bacterial antiserum has been produced by repeated intravenous injections of live bacteria. Although the significance and specificity of this lesion is by no means clear, it is considered to be compatible with that of hyperergic inflammation.

The bizarre manifestations of the disease as it unfolds clinically have given rise to much speculation regarding its etiology. Stokes,[8] in 1932, described the victim of disseminated lupus erythematosus as "first and foremost an allergic person explosively and furiously responsive to his infection with a broken or inhibited leucocytic defense." The peculiarities in the behavior of the patient with lupus have long been noted, and their interpretations have stimulated controversy.

Therapy with certain agents, such as gold salts, x-rays, drugs, skin applications, vaccines and serums, is said to offer hope in some cases, but in others precipitates violent reactions and tragic results.[16–18] The intolerance to sunlight is well known and documented. The tuberculin reaction is most frequently negative in these cases, which may again represent an immunologic imbalance since the patients are almost invariably adult. In some cases reaction to tuberculin administered intracutaneously is explosive, and has been known to be fatal.[19, 20] The Wassermann reaction very frequently becomes positive during activity of the disease without evidence of syphilis being present,[21] again representing abnormal antibody content.

Hyperglobulinemia is a constant occurrence in lupus, as found by Coburn and Moore,[22] and the erythrocyte sedimentation rate rises to levels much higher than those usually seen in infections, achieving the ranges seen in multiple myeloma, lymphopathia venereum and other high globulin syndromes. Electrophoretic analysis of the plasma fraction showed the gamma globulins to be elevated and the other globulins normal. This pattern is also found in hyperimmune horse serum, apparently representing antibody. The antibody for the Wassermann reaction is apparently also in this electrophoretic area.

Again illustrating the overwhelming antibody response elaborated in the lupus syndrome, Callender et al.[23, 24] report their extensive investigation of a patient who received a series of transfusions and developed "a remarkable series of antibodies in her serum." They demonstrated that she had immunized herself against the bloods of eight different donors with the formation of one familiar and three new antibodies, thereby exhibiting an extraordinary sensitivity to antigenic differences with a remarkable liability to undergo isoimmunization.

The occurrence of the disease almost exclusively among female patients between puberty and the menopause appears to bear no relation to the sensitivity state. It is, however, suggested by many isolated observations that a hormonal factor is of some importance in this regard. For example, it has been shown that the Schwartzman phenomenon can most easily be induced in the pregnant laboratory animal.[11] French investigation has demonstrated that the duration of the anaphylactic state can be altered by the removal of the ovaries in the rabbit,[25] and a synergistic effect is suggested. It has been reported that in the occasional male patient developing lupus the urinary excretion of 17-ketosteroids is low, and the follicle-stimulating hormone high,[26] suggesting hypogonadism with increased estrogen-androgen ratio. Premenstrual exacerbation of the disease has been reported,[26] and improvement following natural or induced menopause has also been observed.[26] Treatment designed at reducing ovarian function has met with good results in some hands and failure in others.

Streptococcus

The case for the streptococcus as one of the sources of the antigen in lupus has received consideration in this country as well as in England. This concept apparently gained favor during the early trial of prontosil in various disease states. It was observed by Barber[27–29] that the use of this new chemotherapeutic drug in lupus was followed in 70 per cent of the cases by such reactions as chills, fever, scarlatiniform eruption and a local aggravation of the lesions. In other diseases drug fever and reaction was not seen in greater frequency than 15 per cent. It was believed that the phenomenon in lupus represented a manifestation similar to the Herxheimer reaction in the treatment of syphilis — namely, a general constitutional response to the toxin and bacterial products resulting from a massive bacterial necrosis. The scarlatiniform rash was described as being typical of that of scarlet

fever and differing from that seen in other sulfonamide reactions. In addition to this observation, it is claimed by Barber as well as others in England[30] and this country[31] that treatment of lupus with the sulfonamides and, later, penicillin has met with dramatic results far superior to any other known therapy, although other reports list such therapy as a failure.[32]

It is further claimed that at least among the cases seen in England streptococcal septicemia is a usual form of death in fatal cases, and that evidence of tuberculosis is usually lacking at autopsy.[29] It is postulated by Barber that disseminated lupus erythematosus represents a nonspecific syndrome capable of being provoked by a variety of bacteria or toxins and that in England this agent is in most cases the hemolytic streptococcus, but that in other vicinities the tubercle bacillus may be of greater significance.

Working with a streptococcus isolated from patients with pemphigus, Welsh[33] was able to demonstrate that the serums from cases of lupus possessed antibodies against the organism. Although antistreptolysin titers are not usually measured in such cases, the titer has been shown to reach significant levels such as 1:640.[34] Denzer and Blumenthal,[35] testing the response to Dick toxin in a case of lupus, found it necessary to raise the dose to 120 units before a positive reaction was obtained. These authors state:

> We do not know how to evaluate this finding. Dr. Dick has advised us that it is unusual, that there are few people who failed to give a cutaneous reaction with such large doses of toxin.

Case Reports

All the cases of disseminated lupus in this series began insidiously with bizarre manifestations before the disease became clinically recognizable. Each case terminated fatally, and in each the diagnosis was confirmed at autopsy. In compiling the case summaries we gathered information from hospital records, clinic charts and files of the training-school office, and the final integrated summary appears to form a meaningful chronologic picture.

The first case presents a pattern in accord with the present-day concepts of the etiology of the disease, whereas the second and third cases are less convincing.

Case 1. J S., an 18-year-old Negress, entered the training school in February, 1938. The history and physical examination were not remarkable at that time, and the tuberculin reaction was negative. In the fall of 1938 tests and inoculations were begun as follows: on October 1, 1938, Schick test (positive on October 5); on October 3, Dick test (positive on October 4); on October 10, 0.25 cc. of typhoid-paratyphoid vaccine (local erythema and fever and malaise for 24 hours); on October 17, 0.5 cc. of typhoid-paratyphoid vaccine (local erythema); on October 24, 0.75 cc. of typhoid-paratyphoid vaccine (local erythema); and on October 31, 1 cc. of typhoid-paratyphoid vaccine (local erythema).

On November 14 the patient received her first injection of 500 skin test doses (S.T.D.'s) of scarlet-fever-streptococcus toxin with no ill results. One week later the second injection of 2000 S.T.D.'s was given and was followed by joint pains and fever. She remained in bed for 3 days at that time, but did not report to the health office. No mention of this appeared on her clinic chart. Nine days later she returned and received the third injection of 8000 S T.D.'s, after which she developed severe arthralgia in the fingers and knees and a sore throat. She was hospitalized for 5 days, during which a low-grade fever was found. Physical findings showed a red throat and a large area of hyperemia extending from the site of the injection on the left arm down the forearm midway to the wrist. Examination of the blood showed a red-cell count of 4,200,000, with a hemoglobin of 80 per cent, and a white-cell count of 7950. The blood Hinton reaction was negative. The urine was normal. She received aspirin with some improvement and was discharged on December 7, with the diagnosis of "Dick-toxin reaction."

She returned to the clinic on December 12, and her inoculations were continued in lower and more gradually increasing doses so that the series included a total of 10 instead of the usual 7 injections, and the highest amount given was 40,000 S.T.D.'s rather than 80,000. These were presumably injected into the deltoid regions of both arms, alternating from left to right. Epinephrine usually accompanied these injections, as follows: December 12, 8000 S.T.D.; December 19, 12,500 S.T.D. (in addition to 0.4 cc. of epinephrine); December 27, 20,000 S.T.D.; January 4, 1939, 25,000 S.T.D. (in addition to 0.3 cc. of epinephrine); January 9, 32,000 S.T.D. (in addition to 0.4 cc. of epinephrine); January 16, 1939, 40,000 S.T.D. (in addition to 0.4 cc. of epinephrine); January 23, 1939, 40,000 S.T.D. (in addition to 0.4 cc. of epinephrine); January 30, 1 cc. of toxin-antitoxin (for diphtheria); February 6, 1 cc. of toxin-antitoxin; February 13, 1 cc. of toxin-antitoxin in addition to 0.4 cc. of epinephrine); and February 20, Dick test (negative).

The patient was re-admitted to the hospital for 12 days in April, 1939, with swelling and pain of the ankles and toes and tenderness of the joints of both hands, which she said had been constant since the Dick-toxin reactions 5 months earlier. An erythematous area with a pustule was present over the right deltoid, which still represented the site of the Dick-toxin injections. At this time urinalysis showed a +++ test for albumin. Examination of the blood demonstrated a red-cell count of 4,250,000 and a white-cell count of 8200. The blood Hinton reaction was negative. The joint pains subsided on aspirin therapy, and the patient was discharged with the diagnosis of "rheumatic arthritis."

Two weeks later the joint pains returned, and the patient developed chills and fever, sore throat and cough. She was re-admitted for 2 weeks 1 month later, at which time one of four Hinton tests was found to be positive, and heterophil antibodies were present up to a titer of 1:64. During this admission streptococcus vaccine was started in small doses, but because of a severe reaction further injections were refused. The diagnoses after this admission were "rheumatoid arthritis and infectious mononucleosis."

During the summer months the joint pains became generalized and persistent, and profound weakness appeared. In September the patient first became aware of a skin eruption over her nose and both cheeks, and the saliva became foul. Examination in the Out-Patient Department in November showed no swelling or redness of the joints. The skin of the cheeks and bridge of the nose was purplish red, mottled and indurated, and some indurated lesions were also found on the upper lip. The lymph nodes were enlarged to visible size in the cervical, supraclavicular, axillary and inguinal regions, and were soft and nontender. The spleen was enlarged to percussion and was palpable on deep inspiration. At this time examination of the blood showed a red-cell count of 3,180,000 with a hemoglobin of 67 per cent, and a white-cell count of 3650. The erythrocyte sedimentation rate was 36 mm. per hour. In addition to albumin, the urine showed occasional red blood cells, white blood cells and hyaline and finely granular casts.

Final admission to the hospital was on November 11, at the age of 19. The eruption had spread to include the anterior portion of the chest, and the patient complained of frequent chills and a temperature rising to 102°F. In addition to the anemia and leukopenia, laboratory examination revealed three positive blood Hinton reactions and two positive gonococcus complement-fixation tests. Heterophil-antibody agglutinations were negative, and tuberculin testing gave a negative result to a dilution of 1:100. On x-ray study

the lung fields remained clear. Clinically, the patient's condition deteriorated rapidly, with a persistently high fever, tachycardia, rising nonprotein nitrogen (to 67 mg. per 100 cc.) and the development of diarrhea. Petechiae developed terminally, and at this time blood culture was positive for *Staphylococcus aureus*. Electrocardiograms remained normal. The patient finally expired on November 20 — 1 year after the Dick-toxin reactions and the apparent onset of the disease.

Post-mortem examination confirmed the clinical diagnosis of lupus erythematosus disseminatus. In addition, the coronary arteries were said to show the changes of periarteritis. Other diagnoses were as follows: bilateral bronchopneumonia; mural bacterial endocarditis of the right auricle and ventricle due to *Staph. aureus*; focal abscesses of the myocardium, epicardium, pericardium and endocardium and kidneys.

CASE 2. E. P., an 18-year-old nurse, entered the training school in August, 1939, in good health. Physical examination at that time was negative, and she received the routine inoculations, which are listed in her clinic record as follows: on September 18, 0.25 cc. of typhoid-paratyphoid vaccine was followed by local erythema and tenderness; on September 25, 0.5 cc. of typhoid-paratyphoid vaccine resulted in a larger and severe local reaction, fever and chills; on October 2, 0.75 cc. of typhoid-paratyphoid vaccine resulted in local reaction of the same severity; on October 9, 1 cc. of typhoid-paratyphoid vaccine caused a small local reaction; on October 19, Dick and Schick tests were given (both were positive on October 20 and 23); on October 23, 500 S.T.D.; on October 30, 1000 S.T.D.; on November 6, 2000 S.T.D.; on November 13, 8000 S.T.D.; on November 20, 25,000 S.T.D.; on November 27, 40,000 S.T.D. and on December 4, 80,000 S.T.D. scarlet-fever streptococcus toxin were administered*; on November 13, a tuberculin test was positive; on December 15, 22 and 29, 1 cc. of toxin-antitoxin (diphtheria) was given; on January 15, a Dick test was given (it was negative on January 17, 1940); on July 8, a Schick test was given, but the results were not read (the patient was away from school); and on September 6, another Schick test was given (this was negative on September 10).

No record of the patient's health is available until April, 1940, when she was admitted to the hospital for 1 week with chills, fever and headache. The temperature was 104°F., and she was found to have edema of the right orbital tissues and firm cervical lymph nodes. The hemoglobin was 71 per cent, and the white-cell count 7900; the urine was normal. A blood Hinton reaction was doubtful at that time, and an x-ray film of the chest was clear. After return of temperature to normal, she was discharged with the diagnosis of "grippe."

Early in 1940 she began to complain of pains in the feet, numbness of the toes and local erythema, and in May of that year she had plantar calluses excised, although her pains were not localized to these parts.

There is no record of the interval from May, 1940, to January, 1941, when she re-entered the hospital with coryza, cough and sore throat. The right orbit was again found to be inflamed, and the cervical lymph nodes were bilaterally enlarged. Examination of the urine was negative. Examination of the blood showed a hemoglobin of 78 per cent and a white-cell count of 8650. At that time the blood Hinton reaction was positive. She was discharged in 24 hours with the diagnoses of "grippe and conjunctivitis on the right." Because of the doubtful blood Hinton reaction in April, 1940, and the positive reaction in January, 1941, the patient was investigated for syphilis after discharge. She vigorously denied the possibility, and no evidence of the disease could be found. Because of ill health and mental turmoil, however, she finally submitted to a course of antisyphilitic therapy under the care of a private physician. The details of this period are not available.

In February, 1943, after graduation, she re-entered the hospital complaining of a cold with chills of 1 week's duration. The temperature was 105°F.

Physical examination showed an injected throat and a large right cervical lymph node and crepitant rales with bronchovesicular breath sounds at the left base posteriorly.

The urine was normal. Examination of the blood revealed a red-cell count of 3,330,000, with a hemoglobin of 67 per cent, and a white-cell count varying from 18,100 to 4100. An x-ray film of the chest showed infiltration in the left lower lobe, which improved rapidly on sulfadiazine therapy. She was discharged in 4 days with the diagnoses of "atypical pneumonia and secondary anemia."

Her next admission to the hospital was in June, 1944. She complained of mild pharyngitis followed by pains in the fingers, left knee and right shoulder. She gave a history of pleuritic pain on three occasions 3 months earlier, stating that chest x-ray films taken atthat time had been normal. Physical findings included large, nontender lymph nodes in the right cervical region and a systolic murmur at the cardiac apex.

The urine again was normal. Examination of the blood disclosed a red-cell count of 3,400,000, with a hemoglobin of 67 per cent, and a white-cell count between 6200 and 10,650. The erythrocyte sedimentation rate showed marked elevation in all tests. Gastric aspiration was negative for acid-fast organisms. X-ray examination of the lungs was interpreted as showing an area of clouding 1.5 cm. in diameter, in the outer zone of the first right interspace, which was considered suspicious of tuberculosis. No bone changes could be identified in the hands. Four electrocardiograms were found to be within normal limits, but PR-interval changes rose to 0.20 second. The infiltration at the right apex cleared, and there was a rise of the hemoglobin to a peak of 75 per cent after liver and iron therapy. She received salicylate therapy and developed a rash. She was discharged in 11 days for rest at home, with a diagnosis of "acute rheumatic fever."

From that time on the patient was aware of a constant fever with occasional bleeding from the gums and palate, weakness and fatigability. She went to Florida in the winter of 1944, and after exposure to the sun she developed and maintained an erythematous, edematous rash over her face, neck and upper back. These areas ulcerated and desquamated over a period of 4 months. The rash gradually faded when she returned to the north, but in the winter of 1945, joint pains returned. In the spring of 1946 she again visited the South and again developed chills, fever, aggravation of the joint pains and return of the rash, which developed a purplish tinge. In July she again entered the hospital for 1 month, presenting a history of chills, with a temperature spiking to 104°F. for 3 weeks. There were also severe generalized joint and muscle pains, excessive salivation and loss of head hair. She had been taking large amounts of aspirin since the last hospital discharge, without effect on the pains. Sensitivity to morphine and codeine had developed, with a reaction shown by vomiting and skin rash.

Physical examination in July, 1946, showed a butterfly rash over the face and anterior part of the chest, and a lymph node, 3.0 by 1.5 cm. in diameter, in the right cervical region. The heart was enlarged, and a loud systolic apical murmur was described. Urine specimens showed occasional albuminuria, with the tests up to ++. Hemoglobin levels ranged between 27 per cent and 52 per cent, and the red-cell count between 1,400,000 and 1,700,000; the white-cell count was maintained between 3000 and 3900, and the blood Hinton test was positive. Cephalin flocculation was ++++, and electrocardiograms were normal. X-ray examination of the lungs was negative, but a calcified lymph node was seen in the right cervical region. The temperature ranged to 104°F. Five transfusions of whole blood failed to effect significant improvement.

Final admission was on August 17. Chills, fever and joint pains continued at that time, and alopecia was well developed. Additional laboratory studies showed a rise in the icteric index to 35, a cold agglutinin blood titer of 1:640 and a positive blood Hinton test. Each attempt at blood transfusion brought violent reactions, with chills and temperature reaching over 107°F., so that it became necessary to prepare her for these transfusions with nembutal and epinephrine, as well as warming of the donor's blood. Temperatures remained irregular up to levels of 105°F. and the patient finally developed convulsions and disorientation and died on September 4.

The findings at post-mortem examination were described as confirming the clinical diagnosis of lupus erythematosus disseminatus, and no evidence of active tuberculous infection was found.

CASE 3. M. S., an 18-year-old nurse, entered training in February, 1942. Her history at that time revealed that in

*No statement about reactions to these inoculations was included in the clinical record.

childhood she had had a vesicular skin eruption and one episode of hives while in grammar school. She also reported profuse menstrual flow with severe dysmenorrhea, often associated with nausea and vomiting. Physical examination was negative, as was the tuberculin reaction. She received the following tests and inoculations:

On March 2, 0.5 cc. of typhoid vaccine was followed by a large area of local erythema with discharge; on March 9, 1 cc. of typhoid vaccine was given, and the arm was stiff and painful for 2 days; on March 16, 1 cc. of typhoid vaccine was given; on March 23, Dick and Schick tests were given — they were negative on March 24 and 27; and on March 30, the tuberculin test was negative.

Three months later, while at the seashore, she fell asleep on the beach and suffered a severe sunburn. When this subsided it left two small erythematous areas symmetrically placed at the outer end of each eyebrow. These slowly enlarged and spread over the nose and cheeks, preserving a remarkable symmetry. She left the training school at this time, but in September she sought admission to another training school. At that time a "facial acne" was described, and a systolic cardiac murmur was reported over the entire precordium. The Schick test was again negative.

In August, skin lesions had also appeared over the right forearm and over the lumbar spine. By December, the facial lesion had spread around the eye to the cheeks and over the bridge of the nose, still preserving symmetry. In January, 1943, she developed an upper respiratory infection with diarrhea, for which she was hospitalized for 2 days. Two months later she became aware of profound anorexia and loss of energy. In May diarrhea returned, this time with sore throat and severe headaches. Physical examination showed congestion of the eyelids, nasal mucosa and throat.

Examination of the blood revealed a red-cell count of 2,910,000, with 60 per cent hemoglobin, which fell to 46 per cent in 2 days, and a white-cell count of 27,000. The blood smear showed the presence of small nucleated red blood cells. The urine contained a few red blood cells and white cells per high-power field, and a trace of albumin.

On May 6, she was hospitalized complaining of swelling of the entire face and puffiness of the eyes, fever and sore throat with bleeding from the nose and mouth. There was some cough, associated with substernal pain. Small ulcerated lesions of the fingertips had been noticed for several weeks.

Physical examination showed a temperature of 103.2°F., a pulse of 146 per minute and respirations of 36 per minute. In addition to the eruption symmetrically located over the nose, cheeks, temples and ears, eroded and bleeding lesions were found on the lips, hard palate, fingertips and toes. The face was puffy and swollen, and examination of the heart showed a rapid rate with gallop rhythm and a systolic murmur along the left sternal border and base.

Examination of the urine disclosed a ++ test for albumin, and the sediment contained 1 to 10 white cells per high-power field. The red-cell count was 2,980,000, with a hemoglobin of 10 gm., and the white-cell count 4050; the total protein was 5.01 gm. per 100 cc., with an albumin-globulin ratio of 2.7:2.3. Throat cultures on two occasions yielded beta-hemolytic streptococci, but the blood culture was negative. Electrocardiograms and x-ray films of the chest were not remarkable.

The temperature ranged between 103 and 105°F., and the patient's course was rapidly downhill. She died on May 9, after an episode of pulmonary edema.

Post-mortem examination confirmed the diagnosis of disseminated lupus erythematosus in addition to bilateral pneumonia and fatty degeneration of the liver.

Discussion

Considering the current speculations regarding the etiology of lupus, it may be of interest that an allergen can be traced as a possible causative factor in each of the cases presented above. The circumstances preceding the onset of the disease in Case 1 indicate a close association between the reactions to the streptococcus toxin and the disease state itself. Indeed, the metamorphosis from one to the other is such a direct and continuous process that it is impossible to outline the termination of the reactions to the toxin and the earliest symptoms of the disseminated disease. Although the patient reacted with severe manifestations to the scarlet-fever streptococcus-toxin injections, the entire series was completed. The rash that appeared on her arm at the site of the inoculation persisted for a year up to the time of death, gradually transforming into the lesions of lupus. The facial lesion became a later manifestation. The joint pains and malaise associated with the reactions never fully subsided and slowly merged into the florid process of disseminated lupus.

In Case 2 no such definite correlation could be demonstrated. If, however, the change in the blood Hinton reaction can be accepted as an early serologic alteration of disseminated lupus, it can be seen that this occurred shortly after a series of inoculations had been completed.

In Case 3 the typhoid vaccination might be considered an associated allergen. It was after exposure to sunlight less than three months later, however, that the cutaneous manifestations of lupus first appeared. Fourteen months after the injections the patient died of lupus, having progressed rapidly through the final stages of the disease.

It is conceivable that an antigen was supplied in the form of a bacterial product in all 3 cases, and in 2 it may have been the streptococcal toxin. This is entirely compatible with the multiple or variable, nonspecific sensitivity concept of the pathogenesis of lupus as a disease of allergy or adaptation.

The local and systemic reactions to the Dick toxin may be severe in 10 to 15 per cent of cases.[36] These are characterized by headache, fever, nausea, vomiting, abdominal distress, sore throat and scarlatinal rashes.[36–38] Local reactions of purplish, mottled and dusky-red erythematous areas,[39] which may achieve some chronicity at times, have been described. Muscle and joint pains are apparently less frequently seen, but according to Healey[40] occur in about 3 per cent of young adults immunized. He demonstrated that the arthralgia in 5 subjects was not produced by the protein contained in the broth used in the preparation of the toxin, and that it was absent when the toxin was destroyed by heat. According to Toomey[38] the person reacting with arthritis is "never desensitized by repeated injections of scarlet fever toxin to the point where he may not have reactions following subsequent increased injections of the toxin."

If such reactions possess a denominator in common with the so-called diseases of allergy and hypersensitivity, it seems possible that there is a point at which the systemic effect of the antigen-antibody reaction becomes irreversible and the disease progresses even if the antigen is removed. Although the situation outlined above is unusual and artificial, it is conceivable that in other cases a constantly present or frequently recurring obscure infection can render the patient sensitive and from that point on supply a bacterial antigen to initiate a series of bodily reac-

tions similar to those supplied by the injections in these 3 cases.

The facts of the cases as presented herein obviously justify no conclusion regarding the etiology of disseminated lupus erythematosus. Can there be an association between the pathogenesis of the disease and allergenic factors?

Summary

The etiologic speculations regarding disseminated lupus erythematosus as listed in the literature are reviewed. There is a trend at present to include this disease among others thought to be associated with allergy and hypersensitivity, although the evidence for this is indirect.

Three cases of disseminated lupus occurring among student nurses are presented. In 1 the apparent onset of the process coincided with Dick toxin reactions. In the others such a direct correlation was not present, but the disease followed similar inoculations by several months.

The possibility that an allergen was present in each of these cases is suggested.

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NECROTIC LESIONS OF THE LEG IN ARTERIOSCLEROSIS*

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BOSTON

IT IS commonly known that necrosis can occur in the toes or feet in the presence of arteriosclerosis. It is the purpose of this paper to indicate that necrosis may likewise start more proximally, in the leg, and that the lesion is of grave import and deserves painstaking treatment. The disorder may arise spontaneously as an infarction of the skin and subcutaneous tissue. In other cases the necrosis follows local trauma or infection.

CLINICAL VARIETIES

Infarction of the Skin

In this category may be placed cases in which there is the sudden appearance of a blue-red area on the leg, which quickly turns black. This is followed in a few days by sloughing and ulceration. The limb shows evidence of high-grade arteriosclerosis, with ischemia of long standing. Such lesions are presumably the result of spontaneous thrombosis in small arteriosclerotic arteries, though the exact mode of genesis is not proved. Small lesions of this type resemble those described by Hines and Farber[1] as "hypertensive-ischemic" ulcers. These writers believe that the local ischemia is due to the arteriosclerosis of hypertension. The mechanism of the necrosis is probably the same as that responsible for many such lesions in the toes. Skin necrosis due to local arterial thrombosis is rare, but may be seen in other parts of the body, such as the trunk and the upper extremities.

The infarct and resultant ulceration may be small or large, single or multiple. Its course is to some extent related to the size of the necrotic zone and the location. Small ulcers tend to heal; the larger ones, with the aid of superimposed infection, tend to go on to massive gangrene. A proximal level is somewhat more conducive to healing than a more distal one.

The following cases are representative of those in this group.

CASE 1. H. R., a 74-year-old man, was seen at the Massachusetts Soldiers' Hospital. He presented three ulcers of the left upper leg of 4 weeks' duration. The lesions had first appeared as painful isolated red spots, which had turned black in 2 days, and had then begun to ulcerate. There was a history of claudication of 10 years' duration, but with no apparent recent change in circulatory status.

Physical examination disclosed three separate ulcers, each about 1.5 cm. in diameter (Fig. 1). The edges were irregular, with gray, sloughing sides and base, and the lesion was surrounded by a narrow red areola. The limb was moderately ischemic. The femoral pulsation was of fair quality, but there was no pulsation below this level. The vascular status of the right limb was similar to that of the involved side.

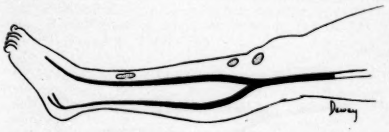

FIGURE 1. *Spontaneous Small Areas of Necrosis in Case 1. There is occlusion of the popliteal and both tibial arteries.*

The blood pressure in the arm was 160/110. There were signs of arteriosclerotic heart disease, but no overt failure.

Treatment consisted of the daily application of wet dressings of tyrothricin solution (0.5 mg. per cubic centimeter). The ulcers improved rapidly and healed in 4 weeks.

CASE 2. E. LeP., a 57-year-old man, was seen at the Massachusetts Soldiers' Hospital for ulceration of the leg of 2 weeks' duration. The involved area had initially turned black and painful and had then broken down. Diabetes was known to have been present for 6 years. It was well controlled by diet and the taking of 15 units of protamine insulin daily.

Physical examination disclosed a slough, 4 cm. in diameter, over the lower lateral aspect of the left leg (Fig. 2). There was evidence of mild infection about the involved area. Pulsations of good quality were felt over the femoral and popliteal areas. There was a faintly perceptible pulsation in the dorsalis pedis artery but none in the posterior tibial artery. Oscillometric examination disclosed moderate reduction in pulse expansion and pressure in the upper calf, but great reduction at the level of the ankle. The foot blanched moderately on elevation. The right lower leg showed a similar vascular status.

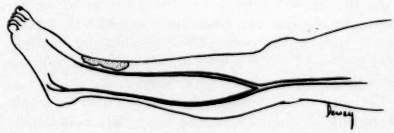

FIGURE 2. *Extensive Spontaneous Ulceration in Case 2. There are patent popliteal, narrowed anterior tibial and occluded posterior tibial arteries.*

Treatment consisted of local dressings of tyrothricin solution and parenteral administration of penicillin. The slough had not separated after 6 weeks of this treatment, and infection about the edges of the ulcer was increasing. A lumbar sympathectomy was advised but refused until 5 weeks later. Sympathectomy was performed and induced a marked increase in blood flow. The slough separated in a week, and the ulcer healed 3 weeks after the operation.

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CASE 3. A. H. P., a 77-year-old man, was referred by Dr. Tracey Roberson, of Ware, Massachusetts, for extensive necroses of the right leg. Ten days earlier a painful, small, black area had appeared on the lateral aspect of the lower third of the leg. It had increased rapidly in size and appeared to be progressing. Varicose veins had been present for many years, but had not given rise to symptoms. The patient had had a severe coronary thrombosis 7 years and a cerebral vascular accident 2 years before the present illness.

Physical examination showed a black, necrotic zone of irregular outline, 10.0 by 8.5 cm., at the junction of the middle and lower thirds of the right leg, mainly on the lateral surface, but encircling about two thirds of the circumference of the leg (Fig. 3). About the ulcer was a red zone of irregular outline, but no great tenderness or swelling. The foot was cold and dry. There was pronounced blanching on elevation. The femoral pulsation was of good quality, but no pulsation was made out below this level. The oscillometer showed a minimal pulsation below the knee, with no pulsation whatsoever at the ankle. There were a few varices in the calf. The vascular status of the left limb was similar to that of the right.

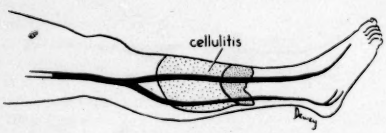

FIGURE 3. *Extensive Spontaneous Ulceration with Secondary Infection in Case 3.*
There is old occlusion of the popliteal and both tibial arteries.

After a few days' observation it was evident that the ulceration was deep and that infection presented a real threat. Amputation was advised. The patient refused, went home and died from spreading sepsis in 6 weeks.

Necrosis Secondary to Trauma or Infection

As in the spontaneous variety, the necrosis following local injury or infection resembles that commonly seen in the toes. The precipitating incident does not need to be severe to set off an advancing necrosis in an arteriosclerotic limb.

Varicose ulcer affords the commonest example of superficial infection of the leg in arteriosclerotic patients. The tissues withstand this chronic form of infection rather well. The ulcers may commonly exist intermittently for many years in the presence of arteriosclerosis without giving rise to gangrene. The lesions will usually heal if the varices are treated by ordinary means. However, one should avoid operative procedures in the lower parts of the leg.[2] Rarely, as in Case 4, necrosis advances outward from a varicose ulcer. The precipitation of the necrosis apparently depends upon a superimposed trauma, an episode of acute varicose thrombophlebitis, the acquisition of a more virulent bacterial flora or further degradation of the arteries by advancing atherosclerosis or arterial thrombosis.

It is important to recognize that trauma and infection can, by themselves, initiate arterial thrombosis (as in Case 6). This reduces further the limited blood supply, and the necrosis of the limb can extend more easily.

CASE 4. R. F., a 74-year-old woman, was referred by Dr. Maurice W. Tolman, of Boston. The patient had had varicose veins for about 40 years and varicose ulcers intermittently for 15 years. After having been healed for some months, the ulceration of the right leg had recurred 4 months before the present observations. It was more painful than usual and had enlarged progressively. For 1 month there had been much pain in the calf and foot, and during the past 3 days the foot had become pale and cyanotic.

Physical examination showed multiple foul-smelling ulcerations in the lower two thirds of the right leg (Fig. 4) The deeper parts of the ulcers totaled about 90 square cm. Here the skin and subcutaneous tissues were black and surrounded by additional superficial ulceration. Culture of the ulcers showed hemolytic *Staphylococcus aureus* predominating, with *Staph. albus*, anhemolytic streptococci, diphtheroids and rare coliform bacteria. The small veins in the dorsum of the foot were prominent, and some did not empty after elevation. Several other areas of static blood pigment were seen on the dorsum. The foot and toes showed a general cyanotic tinge, which slowly changed to a blanching after elevation. There was deep tenderness of the foot and calf. No pulsation was made out below the femoral level. The oscillometer likewise revealed no pulse expansion from the upper calf down.

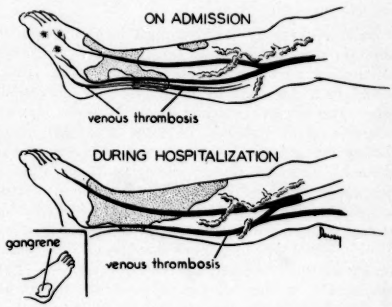

FIGURE 4. *Necrosis Extending from Varicose Ulceration in Case 4.*
On admission there is old occlusion of the popliteal and both tibial arteries and early, deep venous thrombosis and blood pigment in the tissues of the dorsum of the foot. During hospitalization, there is extension of necrosis, extension of venous thrombosis and gangrene of the heel.

It was apparent that the necrosis of this ischemic limb was complicated by spreading sepsis and deep venous thrombosis of the leg and foot. Thrombosis was also suspected in the finer skin vessels of the dorsum of the foot, and in the deep arteries of the leg and foot.

The patient was given penicillin and sulfadiazine, as well as heparin in Pitkin's menstruum. Dicumarol was soon substituted for the heparin. Wet dressings of tyrothricin solution were applied to the leg. The superficial ulcerations showed a tendency to heal, but it became evident that the slough had extended to the deep fascia in several places. In spite of the chemotherapy, intermittent fever continued. A large zone of gangrene appeared on the heel.

A low thigh amputation was advised and performed. The femoral vein was free of thrombus, but there was thrombosis in a large vein in the posterior compartment of the thigh. Microscopical examination showed capillary thrombosis in the superficial tissues of the ulcer (Fig. 5).* The popliteal

*In my opinion, such thrombosis may extend to the veins of the extremity, inducing extensive thrombophlebitis.

artery was almost completely occluded, mainly by extensive atheroma, with further narrowing due to hemorrhage within the atheroma. The popliteal vein showed thrombosis. Unfortunately, sections were not made of the vessels of the leg or foot, leaving unproved the clinical impression of thrombosis in the arteries and veins of these parts.

Dicumarol was given postoperatively, but the prothrombin time was not consistently maintained at low levels. The

FIGURE 5. *Tissues in Case 4.*

The upper photomicrograph of the edge of ulceration shows extensive purulent inflammation, with thrombosis of the small vessels in the ulcer bed and extensive proliferative phlebitis without thrombosis in a subcutaneous vein (hematoxylin and eosin stain, x50). The lower photomicrograph shows the popliteal vessels. The vein on the right shows a completely occluding thrombus. The artery on the left shows extensive atheroma, the narrowed lumen being further reduced by hemorrhage within the atheroma at H *(Verhoeff's elastic tissue stain, x15).*

stump and the buttock swelled considerably, suggesting an upward progression of the thrombosis to the common iliac vein. A small slough of the wound edges occurred and required 8 weeks to heal.

After discharge from the hospital, the patient complained of severe phantom pain. On three occasions a deep abscess formed in the stump end and drained spontaneously through

FIGURE 6. *Necrosis Following Trauma in Case 5.*

There is old occlusion of the popliteal and both tibial arteries. Varices are present.

the scar. A roentgenogram will be taken to determine whether osteomyelitis of the femur is present.

CASE 5. J. McC., a 58-year-old man, was seen at the Vascular Clinic of the Boston Dispensary for an ulcer of the right lower leg. Four weeks earlier he had bruised this area on a hand truck, and the ulcer had formed in a few days. Varicose veins had been present for 5 years, dating back to a deep thrombophlebitis after compound fracture of the leg. Ulceration had never previously been present.

Physical examination showed an ulcer, 4 cm. in diameter, on the medial surface of the right lower leg (Fig. 6). It was surrounded by a wide inflammatory zone. Beyond the involved area, the skin was atrophic, dry and shiny. The foot blanched markedly on elevation. The femoral pulsations were of good quality, but there were no pulsations below this level. The oscillometer showed a barely perceptible pulse expansion from the upper calf downward. Large varices were present.

A right lumbar sympathectomy and a division of the saphenous vein in the groin were carried out. The ulcer showed immediate improvement but required 3 months to heal. During most of this time, however, the patient was ambulatory and at work.

CASE 6. E. W., a 74-year-old woman, was referred by Dr. Paul Hecht, of Braintree, Massachusetts, for ulceration of the right leg. One week earlier, while working in her garden, she had been stung on the leg by an insect. A virulent cellulitis developed, involving the entire leg and associated with chills and high fever. The patient was extremely ill, but improved after large doses of penicillin and sulfadiazine given

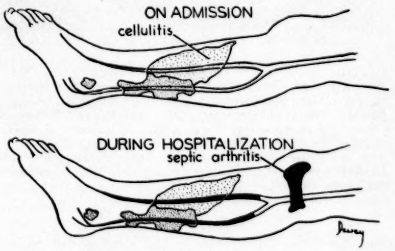

FIGURE 7. *Necrosis and Secondary Arterial Thrombosis Following Infection in Case 6.*

On admission, the major arteries were patent. During hospitalization, thrombosis developed in the tibial arteries, and the knee joint became infected.

orally. Extensive slough of the skin developed, and it was evident that the cellulitis was continuing deeply, though its superficial spread had been halted.

Physical examination disclosed the patient to be in good general condition. Extensive deep slough and cellulitis were present on the medial surface of the right leg, in areas from the ankle to the knee (Fig. 7). The dorsalis pedis and posterior tibial pulsations were present and only slightly reduced in volume. The foot showed no evidence of diminished blood flow. Culture of the lesion showed *Bacillus subtilis* predominating, with a hemolytic *Staph. aureus* and a nonhemolytic *Staph. albus*.

It was hoped that with increased doses of sulfadiazine and parenterally administered penicillin, ultimate separation of the slough and a satisfactory base for skin graft might be obtained. In spite of adequate chemotherapy a low fever continued. On the 5th day after hospitalization the knee joint appeared distended with fluid, though not tender. The pedal pulses were no longer palpable, and the foot was ischemic.

Amputation was advised and performed above the femoral condyles. The popliteal artery and vein were patent. The knee joint was found distended with pus, and the ampu-

tation was therefore left open. Five days later a secondary suture was done. Healing was satisfactory.

Microscopical examination showed extensive arteriosclerosis in the popliteal, anterior and posterior tibial and in the peroneal arteries (Fig. 8). It was confirmed that acute thrombosis had taken place in the anterior and posterior tibial arteries.

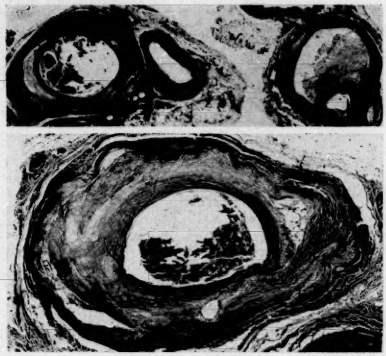

FIGURE 8. *Tissues in Case 6.*

The upper photomicrograph of the posterior tibial artery on the left shows atherosclerosis with acute thrombosis, and the peroneal artery on the right is occluded by an old atheroma (Verhoeff's elastic tissue stain, x20). The lower photomicrograph of the anterior tibial artery shows extensive atherosclerosis with acute thrombosis (Verhoeff's elastic tissue stain, x50). In both sections the apparent incompleteness of thrombosis is due to an artifact.

CLINICAL MANAGEMENT

In many respects the management of patients with necrosis is the same whether the lesion is located on the leg or on more distal parts. It is clear that the presence of infection and thrombosis must be kept in mind constantly. The advanced age of the patient and the presence of marked arteriosclerosis favor these pathologic processes. The tissues limit infection poorly, so that cellulitis and extension of the necrosis are common, and septicemia is a constant threat.

Thrombosis is encountered in a variety of vessels. Microscopical examination of the necrotic areas often reveals red agglutination thrombi in the surface capillaries. These may sometimes be followed into the subcutaneous veins and arteries. The process is often purulent and suggests a basis for septicemia. Thrombosis of the large deep veins is common, as noted by Veal[3] in gangrene from any cause. This process is usually bland at the popliteal level and aids in limiting the purulent phlebitis of the finer vessels. Organization is slowed in old age, especially in the presence of ischemia. Pulmonary embolism may therefore be expected with unusual frequency. Thrombosis of the major arteries may likewise occur in the course of the illness, further limiting blood flow.

Except for small spontaneous ulcerations, necrosis of the leg in the presence of arteriosclerosis calls for treatment in a hospital. If ischemia is pronounced, and the necrosis is widespread and deep, immediate amputation appears most logical. Acute spreading infection is likewise an indication for amputation, but an attempt should first be made to control the infection by appropriate and intensive chemotherapy.

One of three types of amputation may be used: guillotine amputation at a low level followed by definitive closed amputation in the thigh; immediate amputation at the high level but with delayed suture; and high amputation with primary suture. Division of both femoral veins should accompany the amputation. My preference is for a division above the termination of the deep femoral vein, but below the circumflex femoral veins.[4] Dicumarol may be given instead, but only if the amputation wound is closed.

Conservative management may be chosen in the hope that the necrosis has not extended deeply, and that the infection will prove controllable. General chemotherapy is of prime importance. Local applications should be bland. In my experience, wet dressings are superior to greasy ones. Tyrothricin solution (0.5 mg. per cubic centimeter) appears to have some advantage over other materials. If venous thrombosis is present, a bilateral division of the femoral veins should be done. If thrombosis is not evident, dicumarol or heparin should be given as prophylaxis.

An increase in blood flow by lumbar sympathectomy may be extremely helpful, but the operation is only occasionally applicable. Sympathectomy should be considered only if there appears to be a good chance of saving the leg. A favorable effect may not be obtained in the very old patient with extensive arteriosclerosis. As a general rule, a good skin-temperature response after spinal anesthesia should be obtained before sympathectomy is performed in patients over fifty-five. This rule should be abrogated if the limb is in jeopardy.

Varices should be treated by high division of the saphenous vein.

In favorable cases these conservative measures may induce healing of the necrotic area. In others, a granulating area may be obtained, which can be skin-grafted, preferably with "pin-point" grafts. It is conceivable that débridement of the necrotic area may occasionally be used as a preliminary to skin grafting.

An opinion regarding the probable outcome of the conservative treatment should be made as soon as possible, generally in seven to ten days. Conservative treatment should be abandoned, and ampu-

tation performed, if it is evident that infection cannot otherwise be controlled, or if the necrosis increases.

Conclusions

Necrotic lesions on the leg in the presence of arteriosclerosis carry the same possibilities of loss of the limb, or of death, as lesions on the toes or foot.

The patients are usually advanced in age, and the arteriosclerosis is severe.

The lesions may arise spontaneously from thrombosis of arteries supplying the skin, with resultant infarction. In others, necrosis follows trauma or infection of the leg.

The prognosis is poor because of infection and secondary thrombosis — the infection is apt to be difficult to control, and the thrombosis, which is extremely common, involves fine cutaneous and subcutaneous vessels in the necrotic area, the deep veins and occasionally the major arteries of the leg.

Amputation is necessary for extensive necrosis, infection incompletely controlled or new areas of necrosis.

Conservative treatment may be tried, but should be abandoned unless a good response is obtained promptly. Adequate and appropriate chemotherapy is necessary. Prophylactic use of anticoagulants may be indicated. Venous thrombosis calls for division of the femoral veins or for anticoagulant therapy. Lumbar sympathectomy is occasionally helpful in obtaining healing.

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ANION EXCHANGE RESINS IN THE TREATMENT OF HEARTBURN DURING PREGNANCY

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HEARTBURN during pregnancy, an annoying symptom with little if any significance in mortality or serious morbidity statistics, is nevertheless distressing to the patient who suffers from it and to the physician who bears the brunt of the complaints. Rodway and Shelley[1] reported this symptom in 66 out of 100 pregnant women, and the experience of most obstetricians tends to corroborate this incidence. The modern theory for the etiology of heartburn states that the regurgitation of gastric contents into the distal esophagus distends the sensitive neural endings of the esophagus. The distention is further enhanced by intermittent spasm of the cardiac sphincter and causes the symptom. Prostigmin has been administered in accordance with this theory of etiology and has afforded satisfactory relief from pyrosis during pregnancy.[2–4] It is rational therapy since prostigmin has been shown clinically and experimentally to increase isoperistaltic contractions in the gastrointestinal tract.[5–7] It is somewhat disconcerting, therefore, to find that anion exchange resins,† admittedly an empiric, unphysiologic therapeutic agent for heartburn during pregnancy, offer qualitative and statistical relief as good as that obtained with cholinergic substances.

Gastric Physiology During Pregnancy

Williams[4] has reviewed the changes in the stomach and its physiology during pregnancy. The normal vertical position of the stomach is altered as the gestation progresses, so that near term the fundus is found under the left leaf of the diaphragm. The greater curvature is forced nearer the cardiac sphincter by a 45° dextrorotation of the axis of the stomach. As the gastric motility decreases and the emptying time increases[8] the tendency to regurgitation by means of reverse waves of peristalsis increases. The increase in atony of the stomach concomitant with advancing gestation involves the cardiac end of both the esophagus and the stomach, resulting in a reflux of gastric contents into the lower esophagus. Gastric acidity decreases with advancing gestation up to the last month before delivery, when it begins to rise again.[9] This fact appears incompatible with the relief afforded from the alkali therapy reported so widely.[10–14] On the basis of the decreased gastric acidity in late gestation hydrochloric acid has been used for heartburn,[10, 15] with relief reported in 76 per cent of 45 patients treated.[12] Experimental distention of the lower esophagus, irrespective of the type of fluid or mechanical agent used, has been demon-

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†The anion exchange resin used was marketed as "resinat" (200 mesh) by the National Drug Company, Philadelphia, Pennsylvania. Chemically, it is a polyethylene-polyamino methylene substituted resin of diphenylol dimethyl methane and formaldehyde in basic form.

strated to cause all the symptoms of heartburn.[4, 16–19] On this basis the modern "neuromuscular theory" of heartburn has been postulated. After secondary intermittent spasm of the cardiac sphincter the normal esophageal wave of peristalsis distends the lower esophagus with its sensitive neural endings. Heartburn results and can be completely relieved by a cholinergic drug in 81 per cent of a total of 43 patients reported.[2–4]

The reported failure to relieve the heartburn in 19 per cent of these pregnant patients may be due in part to the presence of unsuspected diaphragmatic hernia, which Rigler and Eneboe[20] have demonstrated in 18.1 per cent of primiparas during the third trimester of pregnancy. They report the incidence of hiatus hernia in pregnancy as 12.8 per cent. This has been corroborated by Evans and Bouslog,[21] Dwyer[22] and Schnepp.[23]

It is of course true that the majority of patients with heartburn have obtained symptomatic relief by using alkalis such as sodium bicarbonate, aluminum hydroxide and block magnesia.[10, 11, 14] The widespread recourse to alkalis attests to the efficacy of this symptomatic treatment, but reports limit relief obtained by alkalis to 50 per cent of these cases of heartburn.[12, 13] Roth[3] believes that the "effect of these alkalis must be largely psychic," and it must be agreed that in view of the hyposecretion of acid that is present late in pregnancy and the equivocal results reported, this may be true.

Table 1. *Data in Pregnant Patients Administered Anion Exchange Resins for Heartburn.*

Case No.	Age	Parity	Duration of Heartburn	Degree of Heartburn	Relief
	yr.		wk.		
1	32	I	32	Severe	Complete
2	24	II	30	Moderate	Complete
3	28	I	33	Moderate	Complete
4	29	I	32	Moderate	Complete
5	33	I	26	Severe	Complete
6	40	II	24	Moderate	Complete
7	21	II	20	Severe	Complete
8	32	IV	22	Moderate	Complete
9	23	I	28	Severe	Complete
10	29	I	16	Moderate	None
11	26	I	30	Moderate	Complete
12	26	II	32	Moderate	Complete
13	27	I	26	Severe	Complete
14	23	I	30	Moderate	Complete
15	18	I	23	Moderate	Complete
16	28	I	14	Severe	Complete
17	30	I	22	Severe	Complete
18	30	II	34	Moderate	Complete
19	29	I	30	Moderate	Complete
20	28	III	18	Moderate	None
21	31	II	33	Severe	None
22	40	I	27	Severe	Complete
23	37	I	18	Moderate	Complete
24	30	II	32	Moderate	Complete
25	23	III	24	Moderate	Complete
26	22	I	36	Severe	Complete
27	24	I	32	Severe	Complete
28	25	II	12	Moderate	Complete
29	24	I	27	Moderate	Complete
30	33	III	20	Severe	Complete
31	29	II	27	Moderate	None
32	21	I	15	Moderate	Complete
33	28	II	31	Moderate	Complete
34	24	I	28	Moderate	Complete
35	27	I	19	Moderate	Complete

Experimental Study

Anion exchange resins were suggested in the management of heartburn in pregnancy for several reasons. They are biologically practically inactive, have no effect on the acid-base balance of the blood, do not cause constipation or diarrhea, have practically no significant toxicity[24] and serve to absorb and neutralize acids.[25] In addition, there is an absence of phosphate ion removal, lack of acid rebound, no chloride removal and effective pepsin inactivation.[26] They were found valuable in the relief of pain associated with peptic ulcer even though the progress of the ulcer was reported to be uncertain.[27]

A total of 35 private obstetric patients with sufficient heartburn of pregnancy to require medication were offered anion exchange resins in 0.25-gm. gelatin capsules for relief of symptoms. The usual dose was two capsules repeated in one hour as necessary. More than two doses were rarely required, and relief was obtained in 31 out of 35 patients who received the medication (Table 1). As a rule the patients reported the disappearance of the epigastric and precordial burning within ten minutes of the time the two capsules of resin were taken. It is remarkable that although most women required medication three or four times a week, more than 40 per cent of those who obtained relief from the medication remained free from symptoms for seven to ten days. All these patients were treated before the last month of gestation since it has been reported that 75 per cent of untreated patients experience spontaneous remission of heartburn in the last month of pregnancy.[1] This factor has been all too frequently ignored in the evaluation of therapy for heartburn in pregnancy.

The average age of the patients in this group was 26.7 years, and it is of interest that 5 of the primiparas were over 30 years old. Twenty-one were primigravidas, 10 secundigravidas, 3 tertigravidas, and 1 a quartigravida. The onset of heartburn occurred in the second trimester in 14 and in the last trimester in 21 cases. Only patients who voluntarily reported moderate (23 cases) or severe (12 cases) heartburn were included in this study. Relief was rapid and effective, and only those who reported unequivocal and complete relief from the heartburn were recorded as such. All patients who reported something less than complete relief are recorded as failures.

A group of 16 patients who obtained relief from the heartburn with the resin were given prostigmin bromide in 15-mg. tablets for subsequent attacks, and the relief was identical with that obtained with resin. The 4 who failed to report relief of heartburn after resin medication were also offered prostigmin bromide tablets, with no improvement in their complaints.

Discussion

The relief of heartburn during pregnancy can be accomplished with variable but almost equal success by both unphysiologic empiric medication and definitive therapy based upon the modern theory of etiology. The administration of anion exchange resins orally for the relief of annoying heartburn in pregnancy has resulted in rapid relief of this symptom in 88 per cent of treated cases. This salutary result is at least comparable to that reported with prostigmin. Cholinergic drugs have been used to excellent advantage in heartburn of pregnancy in accordance with the neuromuscular-dysfunction theory now accepted by most physiologists. Yet this therapy appears to be no more effective qualitatively or statistically than anion exchange resins. This consideration suggests that there is still much to be explained in the etiologic picture of heartburn during pregnancy. The reports of relief obtained from the administration of yeast, thiamine chloride and nicotinic acid[28] and miscellaneous medication[15, 18, 19, 29, 30] merely add to the confusion. Between 8 and 20 per cent of the failures to obtain relief with any medication may be attributed to the presence of an occult diaphragmatic hernia that is reduced spontaneously post partum.

The fact that 88 per cent of the patients treated for heartburn with resin obtained complete relief makes it very unlikely that the mechanism was psychogenic. Rather, Bartlakowski[31] has reported that 70 per cent of esophagi studied microscopically showed islands of gastric-secreting mucosa in the distal segment. It is suggested that these gastric glands secrete sufficient acid and pepsin locally to complement that derived from the reflux of gastric juice and sufficient to discharge the sensory nerve endings of the lower esophagus, which have been primed by mechanical distention demonstrated to be present. The pepsin-inactivating role of the anion exchange resins employed in this study may play an undetermined part in the effectiveness of this medication. The resin is recommended because of its value in control of heartburn during pregnancy, its freedom from toxicity and its economy.

Summary

The etiology of heartburn in pregnancy, present in approximately two thirds of pregnant women, is believed to be a neuromuscular dysfunction of the esophagus and stomach.

Thirty-one out of 35 pregnant women with heartburn obtained complete relief from oral administration of anion exchange resins administered before the last month of gestation.

This unexpected result with an admittedly irrational, unphysiologic agent suggests that the modern theory of the etiology of heartburn has some undetermined defects.

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PRELIMINARY OBSERVATIONS ON THE USE OF HUMAN ARTERIAL GRAFTS IN THE TREATMENT OF CERTAIN CARDIOVASCULAR DEFECTS

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FOR many years surgeons have felt the need for some technical procedure that would help in bridging gaps of the arterial system when a large vessel has been destroyed by trauma or has become thrombosed because of degenerative disease or embolism, or when certain cardiovascular abnormalities require operative correction. Extensive investigations have been conducted to further the work of other experimenters and to determine the feasibility of transferring a segment of large artery from one animal to another of the same species. Full reports of these studies will be published elsewhere.[1-3]

In the laboratory for surgical research sections of abdominal aorta were removed from donor dogs and were subsequently used to replace sections of the abdominal aorta of recipient dogs. Sixty-three such grafts were made, employing mongrel dogs. The studies were made in three sets of observations: vessels were removed from donor animals and implanted within a few hours into recipient dogs; segments of aorta were frozen and kept for varying periods before being implanted; and arterial segments were preserved for varying periods by storage in special nutritive solutions just above freezing before being placed in recipient animals.

In the first set of studies, there were twenty-seven grafts. After removal, the aortic segments were kept moist and in a common, domestic refrigerator for periods varying from two to seventy-eight hours, and were then grafted into recipient dogs. These recipient animals were kept under observation for as long as a year. When the segments for the grafts had been kept for only a few hours, there was a very high probability of their survival in the recipient animals. When segments were kept for about six hours and then implanted, only about two thirds of the grafts survived and remained in satisfactory condition. When specimens of aorta were kept from eighteen to seventy-eight hours before being implanted into recipient animals, the vast majority of the dogs died from thrombosis in the grafts or from rupture at the suture lines.

In the second set of studies, blood vessels from the donor dogs were rapidly frozen to —72°C. and were stored at this temperature for periods varying from two to thirty-five days before being implanted into recipient dogs. Twelve such grafts were made. Three quarters of these dogs died within five to thirty days from hemorrhage at the suture lines. Two grafts became partially thrombosed. One animal was kept for six months, and at autopsy the graft showed moderate intimal sclerosis. These results led to the firm conviction that storage of vessels by freezing would not be a satisfactory method for preserving arterial grafts.

In the third set of studies, aortic segments were taken from donor dogs and stored in flasks, the vessel being just covered with an electrolyte solution, to which had been added glucose (1 per cent) and dog serum (10 per cent) and a buffer, as well as penicillin and streptomycin (giving a concentration of 50 units of each per cubic centimeter), and finally a phenol-red indicator so that changes in the reaction of the solution could be determined by inspection of the fluid in the flasks. Each flask with its solution containing a segment of vessel was stored in an icebox, the temperature of which did not range beyond 1 to 4°C. Tissue-culture studies on segments of vessels preserved in this way showed that vessels were viable for as long as thirty-five to forty days in most cases. Segments of vessel that had been stored in this manner for periods of from two to ninety-eight days were implanted into recipient dogs. Twenty-four such grafts were made, and the recipient animals kept from four days to ten months. There were no deaths from dehiscence or thrombosis of any of the grafts. Three animals had minor thrombi at the lines of anastomosis. The grafts were known to be carrying blood for periods as long as ten months. These vessels were studied in the living dogs by aortagrams, and were carefully studied at autopsy after death or sacrifice of the animals. The experiments indicated that arteries can be stored satisfactorily by this method in the cold for slightly more than a month and can still be used for purposes of grafting.

With the above summarized information from the experimental laboratory, it was believed that the last described method of arterial preservation might be applicable for vessel grafting in human subjects. Segments of arteries obtained within a few hours from human beings who had died in automobile accidents were collected under aseptic conditions and stored for use whenever the need for an arterial graft might arise in a human patient. Nine such grafts were used to bridge gaps between the aortic system and the pulmonary artery when

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it was desired to establish an aorta-pulmonary artery shunt for alleviation of the cyanotic state of tetralogy of Fallot, and when it was impossible directly to anastomose vessels of the aortic and the pulmonary systems by the Blalock or the Potts technic. One of these patients died twelve days after operation, largely from the effects of dicumarol therapy. A second died two days after operation from cardiac decompensation. The grafts in both cases were patent at post-mortem examination. In the 7 surviving patients the grafts are apparently carrying blood and have been in place from one to five months. Evidence that these grafts are patent can be adduced from the fact that all the children have continuous murmurs, which previously did not exist, and that the cyanotic states have been markedly improved.

In 3 additional patients, segments of preserved human aorta have been used as grafts during surgical correction of coarctation of the thoracic aorta. Although it is usually possible to excise a narrowed segment of aorta and directly anastomose the remaining ends, removal of the constricted areas from these 3 subjects left very long gaps in the aorta, which precluded reuniting the remaining aortic ends. In each case a graft about 5 cm. in length was employed, and in each case a lumen of full size was established for the aortic pathway. All 3 patients survived operation; they have had relief of the hypertension that preoperatively existed in the upper portions of their bodies, and they have now developed a greatly increased blood flow to the legs. These grafts have been in place only two or three months.

It is too soon to give any final evaluation of the technic of blood-vessel grafting in human cases. However, the early postoperative results are very encouraging, and they certainly warrant further trial and study when no other means are available for satisfactorily bridging a gap in a large vessel of the arterial system.

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MEDICAL PROGRESS

BLOOD AND ITS DERIVATIVES (Concluded)*

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BOSTON

Albumin (Fraction V)

Shock. As the product whose preparation was responsible for the initiation of the entire fractionation program,[9, 11, 213–217] albumin remains of first importance, but its use in the treatment of shock has become secondary. Tested successfully in civilian cases[215–222] of shock, it proved to be a satisfactory therapeutic agent under field conditions.[11, 223, 224] Unless extra fluid was given, however, dehydrated patients received less benefit from the concentrated material than normally hydrated patients did.[214, 218, 221] Various investigators have reported plasma-volume increases due to albumin of 8 to 18 cc. per gram under different conditions. These are summarized in Table 4. Albumin uniformly produces a rise in right atrial pressure and usually causes the hematocrit to decrease. Its effect on cardiac output varies. For civilian use concentrated albumin is a convenient, easily transported, immediately available, stable, safe and effective agent for the emergency treatment of shock and is useful in accident rooms and ambulances and in doctors' bags.

Hypoproteinemia. Considerably less agreement exists regarding the action of albumin in chronic hypoproteinemia.[216] Single injections of 25 gm. in nephrotic patients, as shown by Luetscher[226] and Thorn et al.,[227] produce a rapid increase in plasma volume (25 to 30 per cent), a rise in colloid osmotic

Table 4. *Increase in Plasma Volume Following Albumin Administration.*

Condition Treated	No. of Cases	Average Increase in Plasma Volume (cc./gm. of injected albumin)	
Calculated from osmotic pressure of albumin[225]	—		18.0
Experimental hemorrhage in normal man:	13		17.7
Heyl[214]	11	17.4	
Stead[218]	2	20.0	
Normal man without hemorrhage[223]	17		12.9
Clinical shock receiving less than 400 cc. of saline solution in addition to albumin:	48		12.8
Warren[215]	3	16.0	
Stead[218]	19	13.7	
Cournand[219]	6	11.1	
Lowell[221]	20	12.0	
Clinical shock receiving more than 400 cc. additional saline solution:	27		15.6
Stead[218]	3	22.0	
Cournand[219]	6	14.2	
Lowell[221]	18	15.0	

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pressure (10 to 20 per cent), a smaller increase in total circulating albumin than the amount injected, a slight rise in circulating globulin, an increase in proteinuria (chiefly albumin and alpha$_1$ globulin) and a slight rise in urine volume without change in chloride excretion or albumin or globulin clearance. Within 48 hours most effects have disappeared, and the albumin has left the circulating plasma without being quantitatively excreted in the urine. Doses of 50 gm. given daily for two to thirty days to patients with chronic Bright's disease are reported by Thorn et al.[227] to produce moderate diuresis best in patients with edema, low proteins, no nitrogen retention and normal blood pressure. This stops when albumin is withdrawn. Others[228] have observed, however, that after sixty to ninety days' treatment diuresis may continue to dryness. Perhaps a spontaneous diuresis was initiated. DeSanctis and Sullivan[229] have also reported a successful remission (six months) and rise in serum protein to normal in a four-and-a-half-year-old boy with nephrosis receiving 15 gm. of albumin daily for sixty days, in addition to a low-sodium, high-protein diet. Similar responses were seen in 4 more nephrotic children still under treatment, 2 of whom lost their ascites on this regimen.

In cirrhosis equally confusing results have been observed. Five patients on low-salt, low-fat, high-protein, high-vitamin and high-liver diets were given 50 gm. of albumin daily for one to ten days by Thorn et al.[230] An immediate diuresis was not maintained, and no remarkable effects on ascites were noted. Patek and his associates[231] report a similar failure in 3 patients with chronic cirrhosis treated thirteen to sixteen days. Apparently, the rate of transfer of albumin from plasma to ascitic fluid increased threefold during treatment.

The largest series of cases of albumin-treated cirrhosis followed the longest time was recently published by Kunkel et al.[232] Using doses of 4 to 80 units (100 to 2000 gm.) of concentrated albumin, they treated 17 patients (5 with ascites of short duration, 4 with long-standing ascites, 6 with severe liver damage following infectious hepatitis or biliary cirrhosis and 2 with low serum albumin but no ascites or edema); 14 of the 15 patients with ascites lost their fluid after albumin. High-vitamin, high-protein, high-calorie diets were given without salt restriction. No difference in action of high salt and salt-poor albumin was seen. Patients with marked portal obstruction, high antidiuretic titers in the urine or long-standing ascites proved most resistant. Those with low serum albumin levels and ascites of short duration (especially after infectious hepatitis) responded most readily. Many patients volunteered the information that they developed a feeling of well-being and increased appetite after albumin. Careful caloric and nitrogen balance studies confirmed the truth of this subjective observation. These results help to explain the failures reported by Thorn and his co-workers[230] and Patek et al.,[231] who used smaller doses for shorter periods, and in the Patek series the most difficult group (ascites of nine to twenty-four months' duration) were being treated. The observations of Armstrong[233] and Gibson,[228] using doses of 500 to 700 gm. of albumin, more nearly parallel those of the Kunkel group.[232]

Obviously, chronic hypoproteinemias are very difficult to affect. The edema of a terminal case of lupus erythematosus failed to respond to 400 gm. of albumin.[234] Acute conditions, however, seem to be more sensitive. Jacobi et al.[235] report the excellent response of 2 infants with erythroblastosis fetalis and edema to 30.0 and 12.5 gm. of albumin, respectively, which produced complete relief of symptoms and permitted survival.

Metabolism. Studying the fate of albumin, Eckhardt and his associates[236] maintained 5 normal subjects on albumin by mouth or vein as the sole source of nitrogen for seven to sixteen days. They observed that 37.5 gm. of albumin was sufficient to maintain a positive nitrogen balance when given by vein, but 50 gm. was required by mouth. After the albumin had been discontinued, the excess disappeared from the circulation on a four-day to six-day 50 per cent disappearance curve, reaching normal levels in three weeks. The addition of tryptophane and isoleucine (two major essential amino acid deficiencies of albumin[237]) did not affect these observations.

Thorn et al.[230] achieved no therapeutic effect when they fed albumin to a patient with cirrhosis. They did observe, however, that the onset of urea nitrogen excretion was delayed several days longer after albumin was administered by vein than when given by mouth. This led Albright and his co-workers[238] to study the metabolism of albumin. Giving an osteoporotic female patient 50 gm. of albumin intravenously daily for twelve days, they obtained the following "nitrogen balance sheet" twenty-four days after the last injection: nitrogen injected 82.94 gm., burned 66.51 gm., converted to protoplasm 8.29 gm. and unchanged 8.14 gm. These figures indicate considerably less conversion to protoplasm, slower burning and more protein storage than was found in 3 patients similarly studied after receiving whole plasma. Whether this is a peculiarity of albumin metabolism or a vagary of this particular patient with disturbed calcium and phosphorus metabolism was not determined.

Mechanism of action. The behavior of injected albumin presents two challenging questions. Where does it go from the blood stream? How is diuresis accomplished in certain cases without a sufficient rise in circulating protein to alter the colloidal osmotic pressure significantly?

Eckhardt et al.,[236] after observing the metabolic experiments just described, hypothesized that al-

bumin diffuses into the lymph,* remains in equilibrium with the blood, and is gradually decomposed into amino acids, which are incorporated into tissue or slowly excreted.

Recently many data have accumulated that cast considerable doubt on the universal applicability of Starling's[240] hypothesis of edema formation and removal. Keys and his associates[241] produced classic starvation edema in 34 normal volunteers on a six months' European starvation diet (49 gm. of protein per day). The total proteins dropped only 0.73 gm. per 100 cc., and albumin-globulin ratios remained essentially unchanged with no evidence of cardiac or renal failure or thiamine deficiency. Govaerts[242] had independently observed the same conditions in 17 starving Belgians. Schemm[243] has pointed out for some time the ease of diuresis and loss of ascitic and pleural fluid in many cases on a high-fluid, low-sodium, 40-gm.-protein diet when 140-gm.-protein diets and plasma intravenously had failed to produce any effect. The absence of correlation between edema formation and albumin levels in nephrosis is also well known.[244–246] (Many have no edema with an albumin of less than 1 gm. per 100 cc.) Ralli et al.[247] and Labby and his coworkers,[248, 249] using intravenous liver extract, have more recently induced disappearance of ascites in chronic cirrhosis without changing the serum protein levels. It is not too surprising, then, to find albumin administration followed by diuresis with no change in serum proteins or to have albumin increase circulating proteins without mobilizing ascitic fluid.

Mankin and Lowell[250] sought to explain Patek's[231] failure to remove ascites mentioned above. In 10 patients with cirrhosis they measured the colloidal osmotic pressure of serum and ascitic fluid, ascitic fluid volume and intraperitoneal hydrostatic pressure, and then varied each of these experimentally. Usually, equilibrium was quickly reestablished between plasma and ascitic fluid after the transfer of a small amount of fluid between them. When the serum colloidal osmotic pressure was increased, however, there was a threefold increase in rate of transfer of albumin to the ascites, thereby preventing any osmotic removal of fluid by the blood. This seems to be further evidence that in many cases Starling's hypothesis has little to do with the persistence of cirrhotic ascites. Certainly, the rapid restoration of equilibrium makes it impossible in such cases to apply Donnan's equilibrium principle and Starling's hypothesis, which depend by definition on a "semipermeable membrane" impermeable to the protein. Inability to by-pass or circumvent the membrane is also implied. Perhaps patients with cirrhosis who have responded to albumin therapy established plasma-ascitic equilibrium more slowly or had portal pressure lowered or peritoneal lymphatic drainage improved.

Blakemore[251, 252] reports that all 4 cirrhotic patients with ascites in whom he created a portacaval shunt for portal hypertension lost their ascites postoperatively, and 3 of these had a persistent postoperative *drop* in total protein and albumin levels. It is interesting that of the 93 cirrhotic patients in 5916 autopsies recently reviewed by Hoffman and Lisa[253] 87 per cent had objective ascites, and 90 per cent of these (78 per cent of the group) had evidence of portal hypertension and obstruction. Perhaps this is more important in cirrhotic ascitic formation than colloidal osmotic pressure changes are.

In nephrosis, fluid imbalance may be due to an entirely different mechanism. Luetscher[254] postulates an excessive tubular resorption of sodium as the basic difficulty, possibly owing to a diminished glomerular filtration rate.† The injection of albumin raises the circulating protein concentration (even though ever so slightly) that draws water into the blood, increasing glomerular filtration rate and thereby diminishing the proportion of sodium resorbed and perhaps moving out some edema.‡ Armstrong[233] tends to favor this explanation, calling it "isosmotic" addition of albumin (sustained increase in plasma volume without increase in edema-fluid osmotic pressure) as opposed to "isometric" (increased edema-fluid osmotic pressure without increased plasma volume), which fails to mobilize edema. Increased capillary permeability or restricted cardiac output may be responsible for the latter condition.[246]

If, on the other hand, one inclines to the theories[259–261] that protein normally passes the glomerulus and that proteinuria is a failure of the tubules to resorb protein rather than of the glomeruli to retain it, one must consider the possibility that the increased filtration and reabsorption of protein following an increase in serum protein might interfere with the simultaneous reabsorption of sodium. Smetana's[262] demonstration of dye-tagged protein resorption by normal mouse and rat tubules and Gunton and Burton's[263] measurement of normal proteinuria as 2 to 4 mg. per 100 cc. call for serious consideration of this theory.

Obviously, much more work is necessary to improve understanding of the role albumin plays in edema and diuresis. Many studies are underway, and the known unpublished data far exceed the published information. Rumor brings no word of a solution, however.

Binding. In seeking an agent to improve the heat stability of albumin, Luck and his asso-

*Li and Reinhardt[239] report that the albumin content of normal rat thoracic-duct lymph is consistently much higher than that of rat cervical-duct lymph or plasma.

†Schweppe and Freeman[255] find that the glomerular filtration rate is routinely depressed in hypoproteinemic plasmapharesed dogs. They did not report sodium studies. On the other hand, Emerson et al.[256, 257] found the inulin glomerular filtration rate increased in some nephrotic children.

‡All studies of renal function must be reviewed in relation to Cargill's[258] preliminary observation that renal blood-flow measurements following albumin administration are one third higher when measured by renal-vein catheterization than when done by indirect technics.

ciates[264–267] showed that considerable protection was derived from the binding to albumin of fatty acids and related compounds, which were anions with a nonpolar group. The effectiveness of this protection increased with chain length up to 12 carbons. This ability to bind other substances was found to be a property of albumin almost exclusively, probably related to its molecular conformation. Although Bennhold[268] had suggested in 1932 that such a mechanism might exist for transportation of substances in the blood, this was the first work to investigate it thoroughly. There are many examples of the usefulness of this property.[269] It may be part of the antibody defense system, coating bacteria to permit phagocytic ingestion (as pointed out under "sludged blood" above). Certainly, it is necessary for the blocking of anticomplementary action of gamma globulin to permit normal complement-fixation reactions. It may also serve to make lipoid hormones water soluble, protect against hemolytic action of fatty acids and possibly salvage valuable blood constituents of small molecular size by preventing the necessity of their filtration and reabsorption. Even osmotic-pressure calculations are affected, since one molecule of albumin can bind six chloride ions.[270]

Davis and Dubos[271–277] have described in a number of communications a very practical application of this property. Seeking to dissolve the waxy layer of the tubercle bacillus with Tween 80 (polyoxyethylene sorbitan monooleate) Dubos found that it stimulated and at other times inhibited submerged culture growth. Relating the inhibition to unesterified oleic acid content, it was found by chance that serum albumin bound the oleic acid and the Tween, and then stimulated growth so that inoculums of 2 or 3 bacteria could be successfully cultured. It is not a growth factor — merely a protecting mechanism enabling growth to become established.

The most recent example of the importance of albumin binding is reported by Tompsett et al.[278] in investigating the clinical failure of penicillin K. Studying X, G, dihydro F, and K, they found that albumin bound them all in varying degrees from 47 per cent for X to 91 per cent for K, checking quite well with the 85 to 90 per cent loss of activity of K in studies in vivo compared with studies in vitro. It is important that all in vitro antibiotic studies include albumin in the medium used.

Miscellaneous. The use of human or bovine albumin in 25 or 30 per cent solution[200] or mixed with plasma 1:4[279] has markedly improved the specificity and accuracy of Rh typing and Rh blocking antibody tests, facilitating the prenatal management of mothers of potentially erythroblastotic children. In like manner Neber and Dameshek[280] used albumin as a diluent in antibody tests of hemolytic syndromes and were able to demonstrate circulating warm antibodies not found by routine methods in 5 of 17 patients.

Another useful new technic involving albumin is reported by Ferrebee et al.[281] and Vallee and his associates[282] for the separation of leukocytes from whole blood by flotation. When two parts of albumin solution of specific gravity 1.079 are added to three parts of heparinized blood and centrifuged, the plasma and leukocytes form a layer above, and the erythrocytes a layer below the albumin. The leukocytes are easily pipetted off and may be separated from the plasma by saline dilution and further centrifugation.

Blood Substitutes

The expense and difficulty involved in large-scale procurement of human blood and its derivatives have stimulated the search for satisfactory substitutes of animal, vegetable or synthetic origin. Janeway and Oncley[14] have summarized the physicochemical and clinical background of this search.

Bovine albumin is chemically most like human albumin, and much effort has been expended to develop it as a satisfactory substitute.[9, 11, 14, 283–287] Unfortunately, a certain amount of antigenicity remains, even in preparations carefully recrystallized many times. Large-scale investigation was terminated in 1942 upon the death of 1 of 60 volunteers receiving 25 gm. each.[286] Myocardial necrosis was found post mortem. Twenty-four of the volunteers developed symptoms ten to thirty-three days after injection, with fever, purpura and hepatic, renal and cardiac damage (as demonstrated by electrocardiographic changes) of varying degree and duration. Many of these never showed demonstrable circulating antibodies to bovine albumin, and some recovered while bovine albumin was still detectable in the blood.

Wangensteen and his co-workers[287] did not encounter this type of reaction and have continued investigation. They recently reported 469 injections to 410 patients with 2.9 per cent immediate and 9.2 per cent delayed reaction — none fatal. Immediate reactions were anaphylactoid or pyrogenic. Delayed reactions occurred in twelve to twenty-four days as urticaria, erythema, myalgia, arthralgia and fever. The severest cases received most relief from intravenous procaine (1 gm. in 250 cc. of saline solution injected over a period of an hour). Seven autopsies of patients dying from other causes showed no disease attributable to bovine albumin. Despite this and despite its effectiveness in shock, they recommend that it not be used until further despeciated. Attempts to relate antigenicity to sulfhydryl and disulfide groups have not been confirmed.[288]

Edwards[289] attempted despeciation of whole bovine plasma by heating to 72°C. for thirty minutes and adding 0.2 per cent formalin and 0.34 per cent ammonia. Cordier and Demirleau[290]

report 100 successful infusions of this material (average dose of 400 cc.), with only 3 per cent reactions — chills and fever and no anaphylaxis on reinfusion ten to fifteen days later. Melka et al.[291] were unable to sensitize animals with it, and found that the treatment had not diminished its osmotic pressure. Hughes, however, was unable by this method or by that of Lewis[292] to lower the reactivity of the recrystallized albumin used by Wangensteen et al.[287]

Gelatin (bovine, fish or modified) has been extensively investigated and reported.[11, 14, 293] It is safe, nonantigenic, effective in the immediate treatment of shock,[294] capable of producing a positive nitrogen balance and not usually deposited in tissue cells.[295, 296] It is rather quickly excreted, however, tends to depress the serum albumin level and has not been extensively investigated in the treatment of chronic hypoproteinemia.

Human hemoglobin and globin were discussed above. There are no reports of attempts to prepare bovine globin for intravenous use.

Both acacia[297, 298] and pectin[299] have been shown to be deposited in liver cells, possibly leading to damage and impaired function. Both leave the blood stream rather quickly.

The following synthetic preparations are also ineffective: glutamic acid polypeptide; sodium glycerol polysuccinate; dextran[300] — a Swedish glucose polysaccharide from beet sugar, with a molecular weight of 100,000, that is safe but completely excreted in twenty-four hours; and a Russian "colloidal infusion of non-anaphylactogenic protein from milk casein"[301] with deficiencies similar to those of dextran. The Russian "plazmol S–25"[302] is apparently a "tissue-therapy" product of human plasma similar to antireticular cytotoxic serum and not a blood substitute.

Amino acids and protein hydrolysates are composed of molecules small enough to diffuse through normal semipermeable membranes and perform little osmotic function. Their metabolic aspects are discussed below.

Human ascitic fluid is used from time to time but is usually too low in protein to be effective. Philippine investigators[303] report success in treating a nephrotic patient with 100 cc. of material heated at 60°C. for two hours. This has not been repeated.

A minimal molecular diameter of 30 angstrom units seems necessary for retention in normal blood vessels. Few proposed substitutes approach this size (Table 3). Until such a compound is discovered, albumin, plasma and blood remain the most reliable therapeutic agents now available.

Protein Therapy

Metabolism

With the increasing number of amino acid and proteinoid preparations available for clinical use, it is important to review certain aspects of protein and amino acid metabolism as a basis for rational clinical therapy.

The usefulness of a protein or amino acid mixture is apparently related to its composition, route of administration and simultaneous carbohydrate intake. Rose[304] demonstrated the "essential" nature of 10 amino acids in the rat (8 in human adults)*: "those which cannot be synthesized by the animal organism, out of the materials ordinarily available, at a speed commensurate with the demands for normal growth." Not until later, however, was it appreciated that for optimal utilization the missing essential acids must be supplied reasonably near the same time that the incomplete protein is ingested or else much of the incomplete protein will not be utilized. A delay of two[305] to six[306] hours between "incomplete" and "essential" acid intake is sufficient to prevent utilization of the former. This may explain why some proteins such as soy bean with satisfactory total amino acid analyses have low nutritive value (some of the essential amino acid components may be more difficult to digest and more slowly absorbed).

Many investigators are beginning to believe that maximal protein utilization depends on factors other than essential amino acids. The "doubly depleted" dogs (anemic and hypoproteinemic) of Whipple et al.[307, 308] could manufacture hemoglobin and plasma protein satisfactorily on the ten crystalline essential amino acids but failed to maintain weight. Womack and Rose[309] and Woolley[310] noted the same difference in mice fed crystalline amino acids as opposed to casein hydrolysates. They believed, however, that both sets grew — only that the hydrolysate group grew maximally. Woolley attributes this property to a peptide or peptide-like substance, strepogenin, separated from highly purified protein by tryptic digestion but destroyed by hydrolysis. Christensen[311] has observed that casein peptides are less readily utilized than free amino acids and suffer considerable loss when given intravenously. Perhaps this explains the observation frequently reported that protein hydrolysates and amino acid mixtures are better utilized when given orally than intravenously.[312–314]

Cannon et al.[305, 315, 316] believe that a critical level of simultaneous carbohydrate intake is required to maintain a positive nitrogen balance on any amino acid intake. Exceeding that, however, the addition of extra calories has no apparent effect, merely adding adipose tissue. They estimate the critical value as 1240 calories for rats or 1500 calories for man per square meter of body surface per day. Kozoll and his co-workers[313] found 1000 calories per day adequate in man.

The question of protein storage has been much discussed.[317] Originally postulated as separate en-

*Leucine, isoleucine, valine, lysine, threonine, tryptophane, phenylalanine and methionine for man, and arginine and histidine for the rat.

dogenous and exogenous "deposits," the concept was changed to one of "dynamic equilibrium," following Schoenheimer's[318] demonstrations with isotopes that body proteins (including tissue and antibody components) are constantly being interchanged. The body protein reserves (some twenty-five to thirty times as great as plasma protein[319]) are capable of great depletion,[317, 320, 321] at times greater than plasma protein levels indicate. This was nicely demonstrated by Localio et al.,[322] who analyzed the protein content of fascia, peritoneum and muscle in 17 controls, 21 debilitated patients and 17 patients with wound disruption. The fascia figures seemed most reliable and averaged 29.00 gm. per 100 cc. for controls and 18.73 gm. per 100 cc. for the wound disruptions. Of the latter group, 11 had total serum proteins over 6.1 gm. and 2 of these even had albumins above 3.7 gm. per 100 cc. Part of the rapid depletion of reserve protein in starvation may be due to the body's effort to obtain certain poorly stored essential amino acids. If they are present in low concentration, the remaining components may be wasted in large quantity to provide an adequate supply of the needed constituent.[323] When an adequate intake of all the essential amino acids was given in addition to a high-protein, high-calorie diet, Emerson and Binkley[324] were able to show in 3 patients that nitrogen utilization was increased two or three times as much as the total nitrogen intake, whereas raising the dietary protein intake could not increase nitrogen utilization any more than the nitrogen intake increased. Apparently the presence of the essential amino acids permitted a more efficient utilization of dietary and body nitrogen.

Use

Kremen,[15] Elman[16, 321] and Ravdin[17] have written excellent reviews on this subject. Blood, plasma, and amino acids can all be used to maintain nitrogen balance. Preoperative protein therapy is especially desirable in surgical patients showing any anemia or hypoproteinemia, since blood proteins rate the highest priority in the "ebb and flow" of protein between organs and blood,[325] and are maintained at the expense of the tissues, thus retarding healing[322, 326] even in patients with apparently high hemoglobin and plasma protein values.[327] Extremely large amounts may be required ordinarily,[328, 329] and in gastric cancer after operation several observers feel that there is a defect in the mechanism for protein synthesis that demands an even greater amount of protein therapy.[330–332]

Considerable interest has been aroused by the treatment of intractable pain in peptic ulcer with casein hydrolysate used by Co Tui et al.[333] In doses up to 0.6 gm. of nitrogen per kilogram of body weight, as well as carbohydrate (12.5 gm. per kilogram daily), they obtained immediate relief in 48 of 164 cases and eventual relief in all but 16 who followed the diet and 18 who could not tolerate it. It is most important that large and frequent doses be given if any acid neutralization is to be obtained.[334]

Reactions

Reactions to blood and plasma were discussed above. Amino acid and protein hydrolysate reactions are chiefly nausea, anorexia, vomiting, thrombophlebitis at the site of the injection and occasionally pyrogenic chills and fever. Apparently, nausea, anorexia and vomiting are more related to composition of the mixture than to speed of infusion or blood level of alpha amino nitrogen or dicarboxylic acids.[335, 336] The only remedy proposed for the thrombophlebitis has been to select one vein for administration, start peripherally and progress up the arm as it closes off.[312, 337] The crystalline amino acid mixtures and a lyophilized casein hydrolysate seemed to be the two preparations freest from reactions of those reported.[313, 335, 336, 338]

Laboratory Methods

Amino Acids

The increasing need for accurate information on amino acids has led to the development of two important analytical methods.

The *microbiologic assay* developed by Snell[339–341] from earlier work by Schopfer[342] is now the most accurate and reliable method available for assaying most amino acids[343] and many vitamins. By the use of the growth requirements of certain bacteria, especially lactobacillus, a culture medium is prepared containing all necessary ingredients except one amino acid, which is to be investigated. This is added in different concentrations to the medium and inoculum in a series of culture tubes and incubated, and the amount of growth obtained is measured by titration of the lactic acid produced. Growth is plotted against concentration to give a standard curve. The procedure can then be repeated with an unknown replacing the standard amino acid, and its concentration can be obtained from comparison with the curve. This method is quite accurate and is now widely used in large laboratories.

A less complicated qualitative method of *paper chromatography* was recently described by Gordon et al.,[344] Consden and his associates[345] and Dent.[346, 347] A small drop of test fluid is spread along a line near the end of a long strip of filter paper (2 by 45 cm.). This end is then placed in a container of phenol and left to hang in a moist chamber until the phenol has progressed down the paper 25 cm. past the test solution. The paper is dried, sprayed with ninhydrin and dried again. The various amino acids have different solubilities and are carried with the solvent different distances, as shown by

the development of purple "spectral" bands permitting identification. A rough quantitative separation can be achieved by the use of a large paper turned 90° after the first "progression" is complete, and placed with the next edge in a different solvent (collidine). This effects further separation at right angles and provides areas for quantitative comparison, especially when "standard mixture" solutions are run simultaneously.

Total Protein

The *copper sulfate* method of Phillips et al.[348] has come to be the simplest and most widely used of the specific-gravity methods for protein determination. It is reasonably accurate[349–352] for routine survey work, the largest error occurring with fatty, lipid-rich plasmas.

A *unimolecular film* method has been recently adapted by Gunton and Burton[263] from Bateman,[353] Gorter and Grendel[354] for use as a simple, economical, rapid clinical micromethod for determining protein in normal urine and spinal fluid. The test fluid is dropped on the surface of a 3 per cent salt solution to form a unimolecular film, and the area occupied by it is measured at standard film pressure. This is done by the addition of a drop of indicator oil and "sweeping" of the surface with a barrier until the oil is compressed sufficiently to produce a standard interference color indicating a standard pressure. Area is proportional to protein concentration within limits. It is accurate to 2 to 3 mg. of protein per 100 cc. The proteins in the urine of 100 normal subjects averaged 3.7 mg. per 100 cc. by this method.

Protein Fractions

The development of a clinically adaptable *electrophoretic* method by Tiselius[355] opened the way to a more accurate differentiation between the various plasma proteins. The clinical information obtained in this way has been summarized by Stern and Reiner[356] and Luetscher.[18] Stimulated by discrepancies between electrophoretic results and those of classic chemical fractionation,[357–366] several groups have run comparative series. Petermann et al.[361] checked 31 patients by electrophoresis and Howe[367] (22.2 per cent sodium sulfate) fractionation. Albumin by the latter method was 7 to 36 per cent higher, closely approximating the sum of electrophoretic albumin and alpha$_2$ globulin, which frequently showed reciprocal changes on serial study. Chow[368] obtained similar results on 198 samples. Protein hydrolysate therapy frequently caused variations in "Howe albumin" not reflected by electrophoresis. Although subject to inaccuracies itself[369] and separating together some globulins (especially beta) that have nothing in common but their mobilities, electrophoresis remains the most reliable yardstick for protein determinations at present available.

The *immunochemical precipitin* method of Heidelberger and Kendall[370] and Goettsch[371] uses rabbit serums sensitized against specific protein fractions, and measures these fractions in blood or spinal fluid by antigen-antibody precipitation and determines the degree of reaction by measuring the nitrogen content of the precipitin produced.[372] It is extremely accurate, and has been completely described in a new book by Kabat and Mayer.[373] Chow[374] has modified it to permit turbidimetric measurements of amount of precipitin.

New methods. Several new technics have been proposed to give a chemical fractionation method for clinical use approximating electrophoretic separation. Pillemer and Hutchinson[359] used methanol to precipitate everything except albumin. This checks within less than 8 per cent of electrophoresis but requires a cold room or cold centrifuge. Milne[375] employed 26.8 per cent sodium sulfate to precipitate globulin and agreed with electrophoresis within 8 per cent, which was closer than Majoor's[376] results using the same method. Popjak and McCarthy's[377] saturated magnesium sulfate method gave approximately the same agreement, or better according to Schwartz.[366] C. Cohn et al.[365] use a 28 per cent sodium sulfite precipitant and colorimetric method[378] to obtain albumin values within 2 per cent agreement with electrophoresis in a small series. Albanese and his associates[379] propose a microcolorimetric method for determining both albumin and globulin involving a Sukaguchi reaction and arginine determination following 22 per cent sodium sulfate precipitation. Unfortunately, they have not reported a parallel series of electrophoretic determinations. Jager et al.[380, 381] have tried 33 per cent ammonium sulfate to precipitate only gamma globulin, which they have followed as a clinical indicator in rheumatic disease.

There remains an urgent need for a new fractionation method adaptable to routine clinical laboratory use so that change in the plasma proteins can be more accurately followed.

Summary

It is hardly possible to summarize a review. Some points, however, deserve re-emphasis.

Blood drawn into cooled bottles containing acid-citrate-dextrose solution (ACD) and maintained at 4-10° C. will, when transfused after twenty-one days' storage, show 80 per cent cell survival for at least five days after transfusion.

By the use of the substitution technic, 350 cc. of Rh— blood can replace 75 per cent of an erythroblastotic infant's blood.

Recipients other than Group O should not be given O blood unless its antiagglutinin titers are less than 1:64 or Witebsky's A and B substances have been added.

The normal erythrocyte life span is probably one hundred and ten to one hundred and thirty days.

All unhealthy people show a tendency for their erythrocytes to stick together and capillaries to constrict, resulting in diminished oxygen supply to various tissues. This is known as blood sludge.

The American Red Cross is supporting a national peace-time blood-procurement program to provide free blood and its derivatives to everyone.

A presumably noninfected person who has received malaria-suppressive therapy should wait at least two years without symptoms before donating blood. No person who has had malaria should ever donate blood to be used whole.

Because of the danger of homologous serum hepatitis, pooled plasma should be used only when nothing else is available. Transmission by whole blood is much less frequent. No satisfactory specific prophylaxis or treatment has been developed. The routine heating of salt-poor albumin at 60°C. for ten hours destroys the hepatitis etiologic agent.

Fibrin foam and film are finding increasing use in all branches of surgery for hemostasis and tissue-defect repair. Recent film uses include eardrum repair and blood-vessel anastomosis.

Antihemophilic globulin found in Fraction I is an effective temporary treatment for hemophiliac bleeding.

Gamma globulin is an effective prophylactic agent against measles and epidemic hepatitis.

Serum iron is carried in the plasma in combination with a beta globulin, which is usually only about 34 per cent saturated. The normal iron-binding capacity is 314 microgm. per 100 cc., and the iron content 106 microgm. per 100 cc.

Some cases of nephrosis and some of cirrhosis have responded to large amounts of albumin (700 to 2000 gm.), but others have not.

Data from the use of large amounts of albumin contribute further evidence that in many cases of hypoproteinemia the Starling hypothesis is inapplicable or of minor importance.

Albumin has a peculiar property of binding to itself many nonpolar anion compounds. This has facilitated the development of an excellent culture medium for tubercle bacilli, since the albumin binds growth-inhibiting oleic acids. It also explains the ineffectiveness of penicillin K in vivo, since the penicillin is 91 per cent bound by albumin. This may also be responsible for the useful role albumin plays as a diluent in many immunologic reactions.

Leukocytes can be almost quantitatively separated from erythrocytes by the use of an albumin solution of proper specific gravity.

No satisfactory substitute for blood has yet been developed. Bovine albumin is most effective but has a 10 per cent reaction rate. Gelatin is nonreactive but is rather quickly excreted.

For optimal utilization, amino acid mixtures should be given by mouth, should contain all essential amino acids and should be accompanied by a minimal carbohydrate intake of 1000 to 2500 calories per day.

Amino acid reactions seem to be related more to composition than speed of administration — crystalline mixtures give least difficulty.

The microbiologic assay and paper chromatography are useful analytic methods for amino acids.

The classic 22.2 per cent sodium sulfate (Howe) fractionation method for determining serum albumin gives values 10 to 40 per cent too high, since it includes alpha$_2$ globulin, which may vary reciprocally with albumin. Several newer methods are presented attempting to rectify this error in routine clinical laboratory determinations.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 34421

PRESENTATION OF CASE

First admission. A fifty-one-year-old retired policeman entered the hospital with complaints of intermittent dysphagia, crampy pains in both calves, which were unrelated to exercise, tight feelings in the left chest, right shoulder and upper arm, and low back pain relieved by lying down, all of eighteen months' duration.

Except for chronic maxillary sinusitis treated ten years previously by Caldwell–Luc operations, he had always been in good health until two years before entry, when he was admitted to another hospital. The complaints at that time were exertional dyspnea and sharp pains beginning at the right costal margin, which radiated to the scapular region. Physical findings were basal rales in both lungs, moderate tenderness in the right upper quadrant, mild jaundice and moderate ankle edema. A Graham test showed a normal gall bladder. An upper gastrointestinal series was normal. An electrocardiogram showed alterations in the ST segments and T waves and absence of the R waves in all the precordial leads. The patient was hospitalized for approximately four months at that time, and toward the end of his stay he first noted difficulty in swallowing solid foods and also began to notice pain and stiffness of the left leg on arising in the morning. The leg pain and stiffness continued, and a year prior to admission he was admitted to another hospital for study. On several occasions he coughed up bloody sputum, and bilateral superficial femoral-vein ligations were done.

Physical examination revealed a well developed and well nourished ruddy man in no acute distress. There was elevation of the left shoulder on inspiration. A few coarse rales were heard at the left base posteriorly. The heart was not enlarged to percussion. There was a Grade I apical systolic murmur. The remainder of the examination was entirely negative.

The temperature was 99°F., and the pulse regular at a rate of 80. The blood pressure was 150 systolic, 100 diastolic.

Examination of the blood showed a red-cell count of 5,380,000, with a hemoglobin of 12.5 gm., and a white-cell count of 10,300, with 75 per cent neutrophils. The sedimentation rate was 1.33 mm. per minute, uncorrected, and 1 mm. per minute corrected. Examination of the urine revealed a specific gravity of 1.024 with a ++ test for albumin, and the sediment contained 1 to 5 white cells and rare hyaline and granular casts per high-power field. A stool specimen was guaiac negative. The fasting blood sugar was 108 mg., the nonprotein nitrogen 28 mg. and the total protein 7.1 gm. per 100 cc. The spinal fluid was entirely normal. An electrocardiogram showed depression of the ST segments in Leads 2 and 3, a flat T wave in Lead 1 and upright T waves in Leads 2 and 3, absent RV_2, prominent QV_2, QV_4 and QV_5, elevated STV_2, STV_4 and STV_5, upright TV_2 and TV_4, inverted TV_5, elevated STVL and depressed STVF.

X-ray examination of the chest showed blunting of the costophrenic sinuses and emphysematous areas in the left lower lobe. The heart was prominent in the region of the left ventricle; the aorta was somewhat tortuous. The cardiothoracic ratio was 14.5:32.5. A barium swallow showed a constriction in the midportion of the esophagus, with moderate dilatation proximal to the constriction. The constriction extended over approximately 2 cm. There was no evidence of shelf formation. Films of the dorsal and lumbar spine were not remarkable.

Esophagoscopy was done, and there was an area of narrowing 32 cm. from the teeth. The margins were fairly smooth but unusually indurated. Biopsies

were taken and reported as acute and chronic inflammation.

During the one-month stay in the hospital repeated barium swallows were done, with little change in the appearance of the lesion. The original complaints persisted, but the patient was able to eat semisolid foods and was only occasionally troubled by regurgitation. Dilatation of the esophagus was started, and the patient was discharged from the hospital.

Final admission (six months later). The patient was seen at approximately one-week intervals over the next five months for bouginage, but despite this was able to eat only semisolid and liquid foods. The pains in the chest, back and leg were constantly present during this period. One week before admission he was seen in the Emergency Ward with complaints of severe, sharp, stabbing pain in the left calf, left lower chest and flank, and right upper arm. At this time it was noted that the blood pressure was 105 systolic, 70 diastolic, but there were no other changes. X-ray study of the chest showed moderate enlargement of the heart in the transverse diameter. There was also moderate fibrosis in both lung fields, but no definite pulmonary edema. Electrocardiograms revealed changes from the previous one with prolongation of the QRS complex, slight elevation of the ST segment and more marked elevation of STV_2, and STV_4 and deeper Q_1 and V_4.

The patient returned home to re-enter the hospital a week later. The pain in the chest had grown steadily worse. It began in the low left posterior chest and radiated anteriorly beneath the rib margins. There was no cough or sputum. The dysphagia had become much worse, and he was able to take only liquid foods. The blood pressure was 100 systolic, 70 diastolic. He suddenly vomited greenish fluid, began to sweat profusely, complained of weakness but no pain, began to breathe rapidly and died within a few seconds.

Differential Diagnosis

Dr. Daniel S. Ellis: It seems to me that up to the time of the second admission we have a fairly clear picture of a patient who had some vascular disturbance in the lower extremities and probably had pulmonary infarction and for some reason developed cardiospasm of the esophagus. The second admission puzzles me a great deal, and I do not know where I am going to end up at this point.

May we see the x-ray films? Is there any evidence of pulmonary infarct or anything that might be called pulmonary infarct in the first chest film?

Dr. Stanley M. Wyman: There are a few scars —linear bands of density. If this represents pulmonary infarct, it is only the old residual scar. In general, the picture is that of a chronically emphysematous chest, with signs of diffuse fibrosis out to the periphery in both lung fields. The diaphragm is low in position; the heart shadow is enlarged toward the left, probably owing to left ventricular hypertrophy. The aorta is quite tortuous for a man of fifty-one. The barium-filled esophagus can be seen through the heart shadow; it can be seen much better in the lateral view of the chest, which shows this area of narrowing just below the carina. On several spot films taken at this time there is a suggestion of a small crater centrally; it is seen on all the films. There is a characteristic shelf formation, and there seems to be a suggestion of a little nodularity in the upper border of the area. The area extends in all about 2 cm. The films taken a month later again show essentially the same picture, but the crater can no longer be so well identified on the large films. However, on the small films, again, there may be a crater in this area. The next film of the chest taken about three or four months after the original examination again shows a rather considerably enlarged heart but no definite change in the pulmonary pattern. Three months later there is an increase in linear shadows in both lung fields, which may be partly due to technic, though it seems a little more than artifact. The last film taken eight days later shows considerable density extending upward into both lung fields and radiating from the region of the hilus.

Dr. Ellis: Was that taken before he died?

Dr. Wyman: I do not know, but I think so.

Dr. Ellis: Is the aorta enlarged in the last film?

Dr. Wyman: It is definitely tortuous.

Dr. Ellis: How about the aorta in these films? Is there any dilatation there?

Dr. Wyman: I cannot say on these films, the reason being that I can see only the right border of the aorta in the posteroanterior view; the left border is hidden by the mediastinum. In the films taken to project the aorta away from the surrounding structures the aorta does not seem wide, but it is definitely tortuous.

Dr. Ellis: Is there any evidence of destruction of the vertebras anywhere?

Dr. Wyman: I do not see it on these films nor did I on some other films of the spine that I have not shown.

Dr. Ellis: I think I will have to attack this from the end of the story and work toward the beginning. The one thing I am certain of is that a large vessel ruptured and that death was due to hemorrhage.

The presenting complaints at the time of entry to the other hospital were crampy pain in the legs and pain in the back and chest, and at that time he was known to have coughed up bloody sputum. Over a period of hospitalization there he developed the gastrointestinal complaints and dysphagia. Without any question it was believed that the chest pain and the bloody sputum were due to pulmonary infarcts because the femoral veins were tied. At no time was mention made of any swelling of either leg or anything more than pain and some stiff-

ness in the calves of the leg. The more I think about this, the more I am inclined to think that there is one possible diagnosis that might explain all the symptoms and signs rather than to say that he had thrombophlebitis, pulmonary infarcts, cardiospasm and chronic coronary-artery disease with ruptured myocardium. Before this diagnosis is mentioned, the possibility of carcinoma of the esophagus must be considered. However, I think that I have no more right at this post-mortem discussion to call this carcinoma than those who treated the patient had at the time he was alive. The x-ray findings at the time he was in the hospital apparently were interpreted as those of a benign stricture or cardiospasm rather than those due to any new growth in the esophagus itself. This was further borne out by the esophagoscopy, and the biopsy taken at that time recorded only inflammatory changes. That, of course, does not rule out the possibility of a malignant lesion deeper than the level from which the biopsy material was obtained. I think that I will say there was a possibility of cancer with nerve-root involvement, and such involvement posteriorly could have explained some of the chest pain and also the leg pain. However, I believe that that probably was not so.

Another diagnosis, although it is perhaps a little far-fetched because of the duration of the symptoms, is that of a dissecting aneurysm with final rupture of the aorta. I have never heard of one giving symptoms for two years before death, but I have heard of some that have gone for a year. The fact that this man had pain in the back, in the legs and in the chest before he developed dysphagia leads me to believe that he might have had an aneurysm. First of all, we know he had generalized arteriosclerosis, and I am going to say that he had an atheromatous aorta and that the presenting symptoms early in the illness were those of early dissection of the aorta. We can even explain the vomiting of blood on that basis. If there was a slow leakage into the lower trachea or bronchus from the aorta, the progressive dysphagia and the difficulty in swallowing in spite of bouginage lead me to believe that there was increasing inflammation of the esophagus. I think that if it had been due to cancer, the lesion would have been visible in some of the films. A mass, a blood vessel and an aorta slightly distended, possibly eroded, might not have shown up in the x-ray film. The final symptoms, which include pain in the arm, in the flank and in the legs radiating around the costal margin, give such an unusual distribution of pain that again I cannot explain it in any way other than by a slowly dissecting lesion of the aorta.

I have considered the possibilities of simple cardiospasm with generalized arteriosclerosis, thrombophlebitis and old pulmonary infarcts. Having considered carcinoma of the esophagus and metastasis to the spine that we have not been able to demonstrate and having considered that he may have had coronary thrombosis and that the final episode was one of ruptured heart, I think I am going to stick my neck out and make a final diagnosis of a slowly dissecting aneurysm of the aorta, which possibly had eroded into the bronchial tree at some stage of the game, causing bleeding, and that it finally ruptured, producing massive, fatal hemorrhage.

A PHYSICIAN: Were the heart sounds weak or strong?

DR. TRACY B. MALLORY: Dr. Scannell, can you answer that?

DR. J. GORDON SCANNELL: I do not remember particularly — our attention was evidently not called to them.

DR. M. ISAACSON: I should like to ask Dr. Ellis what he thinks of the possibility of aneurysm of the posterior wall of the left ventricle on the basis of infarct causing esophageal constriction. A few cases have been reported, and I* recently reported a case of myocardial aneurysm causing esophageal obstruction. This case is similar.

DR. ELLIS: I think it is a distinct possibility. The reasons for thinking it probably is an aortic rather than a myocardial aneurysm are the slowly progressive symptoms over a long period and the distribution of pain. He may well have had a ruptured myocardial aneurysm.

DR. WYMAN: From the x-ray point of view the diagnosis of cancer is quite feasible. We have seen a good many that did not show definite shelf formation but merely narrowing with or without ulceration centrally. I wonder if the last chest film does not suggest lymphatic spread of metastases to the lung fields.

DR. JACOB LERMAN: I would like to ask if a circular constriction of that sort could be explained on the basis of aneurysm, with pressure on one side, anterior or posterior. It is hard to conceive of an aneurysm producing that picture.

DR. WYMAN: It would not usually unless associated with inflammatory reaction and constriction.

CLINICAL DIAGNOSES

Coronary occlusion.
Stricture of esophagus, unknown etiology.

DR. ELLIS'S DIAGNOSIS

Dissecting aneurysm of aorta, with rupture.

ANATOMICAL DIAGNOSES

Coronary arteriosclerosis, with thrombosis.
Myocardial infarction, left ventricle.
Acute bacterial endocarditis, mitral valve.
Benign stricture of esophagus.
Lipoid pneumonia.
Arteriosclerosis, general.

*Isaacson, M. Myocardial aneurysm causing esophageal obstruction: report of case presenting double cardiac aneurysm with severe dysphagia necessitating gastrostomy. *New Orleans M. & S. J.* **100**:568-573, 1948.

Pathological Discussion

Dr. Mallory: The very widespread, bizarre distribution of pain was suggestive of dissecting aneurysm to me when I read the story over. I do not believe we have an adequate explanation for the pain because the patient did not have a dissecting aneurysm nor did we find anything else to account for it. He had a markedly sclerotic aorta for a man of only fifty-one, if he gave his age correctly; but there were no ulcerations or aneurysmal formation. He had a greatly hypertrophied heart, which weighed 720 gm. There were occlusions in both left descending and right coronary arteries, and there was a large area of infarction involving the lower third of the left ventricle and of the interventricular septum. The complete surprise was the presence of acute bacterial endocarditis of the mitral valve. There is nothing in the history that would remotely have led one to think of such a diagnosis. The obstruction of the coronary arteries could have been due to embolism from the cardiac vegetations or to ordinary thrombosis secondary to atheroma because he had severe atheromatous changes. I favor the latter. The progressive changes in the lungs, which Dr. Wyman has brought out in this series of x-ray films, we did explain. There was extensive lipoid pneumonia of the type seen following aspiration of liquid paraffin. It was sufficiently chronic to have produced much pulmonary fibrosis. This is a fairly common pulmonary complication in patients who have difficulty in swallowing, whether it is due to organic obstruction or to muscular weakness.

Dr. James Heyl: About how old was the process?

Dr. Mallory: It was a matter of months, possibly longer. It is not uncommon, in some of these cases, to see some of the oil transported to other parts of the body. We see it frequently in the spleen. This is the first time I have ever seen it in the liver. Many vacuolated phagocytes were present in the portal areas and sometimes within the lobules. The esophagus showed perfectly normal mucosa except for a small area of ulceration, but the subepithelial tissue was greatly thickened and fibrous, with some infiltration of monocytes and plasma cells.

Dr. Alfred Kranes: Was there any gastric mucosa?

Dr. Mallory: None was visible, and I believe the lesion was too high to make such a possibility likely.

Dr. Ellis: What about the legs? Did the patient have thrombophlebitis?

Dr. Mallory: We have no evidence. They showed nothing externally. There were no pulmonary infarcts.

A Physician: What did he die of?

Dr. Mallory: Acute heart failure.

Dr. Kranes: How do you account for the sudden change after eight days if the coronary-artery disease had been present a long time?

Dr. Mallory: We do not know how long the bacterial endocarditis may have been present or how much pulmonary insufficiency contributed to the fatal outcome.

CASE 34422

Presentation of Case

A forty-three-year-old lawyer was admitted to the hospital because of persistent cough and fever.

The cough and fever began five months before admission, following a prefrontal lobotomy. X-ray studies showed patchy mottling of the left-upper-lung field. There was little response to penicillin, and three months before admission another x-ray film showed extensive consolidation in the upper half of the left lung with a central, clear area 4 cm. in diameter at the level of the second anterior rib. The mediastinum was displaced to the right. A week later multiple cavities could be seen in the left-upper-lung field. The patient continued to run a fever and leukocytosis and developed a marked anemia despite two blood transfusions.

Three years before admission the patient became depressed, with suicidal tendencies. Electric shock therapy resulted in improvement for a year, but symptoms recurred and a frontal lobotomy was performed.

Physical examination revealed an emaciated man with moderate edema of the face, eyes and sacrum. There were patchy areas of scaling and hyperkeratosis over the extensor surfaces of the extremities. The tongue was smooth and glossy. The trachea was shifted to the right. Over the upper half of the left lung there were dullness and bronchial breathing, with flatness and absence of tactile fremitus and breath sounds in the lower half. The liver edge was questionably palpable.

Examination of the blood revealed a white-cell count of 18,200, with 89 per cent neutrophils, and a hemoglobin of 11.5 gm. The total protein was

6.7 gm. per 100 cc. The urine gave a ++ test for albumin, and the sediment contained 10 to 12 white cells and 3 to 4 red cells per high-power field. An x-ray film of the chest showed the left side obscured by homogeneous density. The heart and mediastinum were displaced to the right.

The patient was oriented but unco-operative and incontinent. On the second hospital day 300 cc. of thick, purulent, nonputrid material mixed with old blood was aspirated from the sixth and eighth interspaces posteriorly and the sixth interspace in the axillary line. A smear of this fluid showed pus cells and clumps of gram-positive cocci. This procedure was repeated on the fourth and seventh hospital days with similar findings. The material was negative for tumor cells and grew out abundant colonies of *Staphylococcus aureus* and nonhemolytic streptococci. The temperature varied from 99 to 102°F. The patient received 192,000 units of penicillin daily. On the eighth hospital day a rib resection was done. The pleura was very thick, but no large cavity was encountered. His condition was unchanged until the third postoperative day, when he was found apneic and in shock, and attempts at resuscitation were ineffectual.

Differential Diagnosis

Dr. W. Wilson Schier: This is the story of a lawyer who developed cough and fever following a prefrontal lobotomy. We do not know the details of the operation or the anesthesia used or how long after the operation the symptoms appeared, but presumably shortly after it. At that time an x-ray film of the chest was reported as showing patchy mottling.

The patient received a course of penicillin, said to be intensive, but for how long or how much was received is not known. This pulmonary process progressed until two months later another x-ray film showed extensive consolidation in the upper half of the left lung, with a 4-cm. excavation on the second anterior rib and, also, homogeneous density of the left-lung field. May we see the films at this point?

Dr. James J. McCort: We have the chest films taken on admission to this hospital. A homogeneous density obscures the entire left thorax so that details of the underlying left lung cannot be made out. The mediastinum shows a marked shift to the right The left leaf of the diaphragm is not seen, but the gas-filled fundus of the stomach is seen to be higher than normal, which indicates that the left leaf of the diaphragm is very high. No evidence of bone erosion or destruction is detectable in the ribs.

Dr. Schier: On admission this man showed evidence of long-existent emaciation and avitaminosis. The swelling of the face and eyes may have been due to partial obstruction of the venous drainage of the upper part of the body.

We are given a single total protein value, 6.7 gm. per 100 cc. He may possibly have had a low albumin. We do not know whether he was hospitalized in a mental hospital or not, but we do know that the tuberculosis rate in mental hospitals is higher than it is in the average population.

Two other thoughts come to mind. Electric shock therapy was given two years before lobotomy. Lung abscesses have been described following shock therapy. The second possibility is primary carcinoma of the lung with cerebral metastases, giving rise to personality change. The long course of events, however, makes these two diagnoses unlikely.

The swelling of the face and eyes may also have been due to chronic nephritis, resulting from focal emboli or focal nephritis in the kidneys. The physical signs are consistent with cavity at the left base and fluid in the left pleural space.

The laboratory data are compatible with an infectious process of long standing and associated anemia. The urinary findings are interesting because of the possibility they raise of metastatic abscesses in the kidneys. The question of a palpable liver edge might be the result of multiple hepatic abscesses. Also, sepsis of this long standing might have given rise to amyloid disease. The description of the sputum is lacking. We do not know whether it was foul or bloody and whether acid-fast organisms were seen.

I think that this man had a lung abscess primarily. I do not believe he had a carcinoma of the lung. Whether he had empyema with bronchopleural fistula, I do not know. Visibility of the abscess, especially on the upper half of the left lung, favors carcinoma or a tuberculous process rather than aspiration abscess.

The fact that the fluid aspirated was nonputrid merely means that no putrefying organisms were present.

The deviation of the trachea to the right is less in favor of tuberculosis. Actinomycosis must be considered in a septic process of this duration. Lack

of response to penicillin favors both actinomycosis and tuberculosis as possible etiologic agents. Response to surgery was no better than to penicillin.

The terminal episode may have been the result of flooding of the right lung with secretions from the left lung and development of a bronchopleural fistula. Massive pulmonary embolus and brain abscess are other possibilities. My final diagnosis is lung abscess, following the original operation, with terminal bacteremia and septic emboli in the kidneys and possibly in the brain. I cannot rule out primary lung tumor, tuberculosis or primary actinomycotic infection.

DR. MCCORT: The high left leaf of the diaphragm is hard to explain. One wonders about phrenic paralysis, favoring tumor. This could have been definitely determined by fluoroscopy, which unfortunately was not done.

A PHYSICIAN: Empyema of long standing might also explain it.

DR. MCCORT: The mediastinum is displaced to the right side. I am not sure that the left leaf of the diaphragm should be elevated if there is fluid under tension above it.

CLINICAL DIAGNOSIS

Lung abscess, with empyema.

DR. SCHIER'S DIAGNOSES

Lung abscess.
Terminal bacteremia.
Septic emboli in kidneys and possibly in brain.

ANATOMICAL DIAGNOSES

Carcinoma of left bronchus, with extension into mediastinum and metastases to cervical, mediastinal and abdominal lymph nodes, liver and right kidney.
Pneumonitis, with abscess formation.
Thrombosis of left jugular and subclavian veins.
Bicuspid aortic valve.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The diagnosis on the wards was the same as Dr. Schier's — primary lung abscess with empyema. At autopsy we found a lung abscess but not primary: it was distal to a tumor of the left bronchus that had grown to fill a considerable portion of the left lung. There were many foci of necrotic tumor and secondary abscess formation beyond the point of obstruction. The tumor had metastasized to the liver and kidney but only with relatively few and small metastases. The liver was not enlarged. The tumor had invaded it and expanded locally through the pleura and involved the pericardium. The phrenic nerve was not specifically sought for but in all probability was involved by the tumor, since it spread through the pleura to the pericardium. A coincidental finding, evidently of no importance, was a congenital bicuspid aortic valve.

We did not have permission to examine the brain, but I think it is rather improbable, as Dr. Schier said, that the cerebral manifestations were due to metastases. I think they were probably due to psychosis.

A PHYSICIAN: Did the kidney show anything other than metastases?

DR. MALLORY: There was slight bilateral hydronephrosis and a very slight degree of chronic pyelonephritis.

Correction. On Page 482, in the last sentence of Dr. Means's discussion of Case 34391, which appeared in the September 23 issue of the *Journal*, the word "heart" was erroneously used for "leg veins." This should have read as follows:

. . . .Taking all the cases of pulmonary embolism with infarction, what percentage would you say come from the leg veins?
DR. MALLORY: What would your opinion be, Dr. Castleman?
DR. BENJAMIN CASTLEMAN: Probably about 95 per cent.

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GREATER BOSTON COMMUNITY FUND

NEXT week the Greater Boston Community Fund begins its annual drive to ensure continued operation of more than three hundred Red Feather agencies. The campaign, which will last for five weeks, will as usual ask the support of all sections of the community.

This year's goal of $6,950,000 is estimated as the absolute minimum that will enable the Red Feather agencies to operate on the same scale as last year. The needs are stated to be greater than ever before. All the eight main fields of service — child care, family service, aid to the handicapped, visiting-nurse and other health agencies, hospitals, service for the aged, youth organizations and neighborhood houses for young and old — are essential to the well-being of the community, and all depend on the contributions made during the campaign. The USO, which has been reactivated at the request of Secretary of Defense Forrestal, will depend in large part on the support given to the Fund.

Doctors daily contribute medical service to many of the Red Feather agencies, but they are asked also to respond as generously as possible to the appeal for financial help made during the campaign. Physicians connected with hospitals will be approached by a chairman or a vice-chairman on the hospital staff, and individual practitioners by the regular volunteer workers either at home or in the office.

There is no question that the enormous service rendered by the Red Feather agencies must continue. This voluntary means of helping others to help themselves represents the American way of life at its best. Doctors are urged to give the campaign all possible support: the Red Feather, symbol of both the worker and the giver, should be proudly worn by physicians as indicating their dual role in the community.

ARTERIAL TRANSPLANTS

THE investigations into the use of arterial grafts presented elsewhere in this issue of the *Journal* by Gross and his associates deserve particular mention. Their importance is measured in terms of the recent development of cardiovascular surgery, to which Gross himself has made such outstanding contributions and in which the necessity for bridging gaps in the arterial system is so urgent; further, the possibility that arterial transplants might be made constantly available for these needs has been suggested by the development of methods of preserving blood, corneal transplants and bone tissue.

These careful studies on the possibilities of arterial grafts have proceeded in orderly fashion. First it was determined, using the abdominal aortas of dogs as test material, that fresh segments of artery could be transplanted from a donor to a recipient animal, that the recipient animal could survive the operation and that the transplanted tissue could be incorporated into the arterial sys-

tem of the host and could perform the function for which it was intended. Here it became evident, as might be expected, that the greater the delay between donor and recipient, the less were the chances of tissue survival.

The development of a method of tissue preservation came next; preservation by freezing was attempted, and it was demonstrated that arterial tissue cannot survive this process. The next experiment consisted of the storing of aortic segments in an electrolyte solution to which had been added glucose, dog serum, a buffer, penicillin and streptomycin and a phenol-red indicator. Segments so preserved and refrigerated at a temperature between 1 and 4°C. remained viable for over a month and were transplanted into recipient animals with a high percentage of successful "takes."

The culminating step, toward which all animal experimentation must be directed, has been its application to the human being. Segments of arteries removed from recent victims of automobile accidents were preserved and stored in the manner described above. Nine such grafts have been used to bridge gaps between the aortic and pulmonary arterial systems in the tetralogy of Fallot, with 7 successful results; 2 patients died soon after operation. Furthermore, 3 grafts have been used without a failure in surgical correction of coarctation of the thoracic aorta.

As medical science has developed blood banks, eye banks and bone banks, so the way now seems clear for the establishment of artery banks. In the great human repair shop that the modern hospital has become, the spare-parts department assumes increasing importance.

THE PHYSICIAN AND THE STATISTICAL METHOD

MANY physicians, particularly those who do clinical research, appear to regard the statistical method as the exclusive property of their colleagues in public health or laboratory research. They often dismiss the exact technic, somewhat defensively, by repeating the time-worn statement that anything can be proved by statistics. In recent years, however, more and more clinical investigators are found to be using statistical tests to examine their data, and it may be that the older view needs drastic revision.

The author of a case report hardly needs to turn to the statistical method to support his presentation, but authors dealing with groups of cases should consider the advantages of proper statistical evaluation of their data. The initial planning of any such study is immeasurably benefited by consideration of certain statistical principles such as those dealing with sampling. The results of well planned work can be displayed to much greater advantage if they are treated statistically than if they are not. For example, an average figure is much more meaningful if the variation around the average is presented along with it. One of the most frequent research devices is to compare treated and untreated groups of cases, and, too frequently, one finds the investigator basing his conclusions on a difference that is more apparent than real. Relatively simple statistical technics for testing the significance of such differences are available, and by the proper application of these tests it can readily be determined whether the result is truly significant or whether it is a chance one. The tests are useful not only in evaluating one's own results but also in determining whether those published by other workers are significant, merely suggestive or clearly unreliable.

One may argue that plain horse sense can do the same thing and that there is no need to resort to a mere sophistic, mathematical device for the purpose. The statistical method, however, properly applied, is in fact more than this and might well be defined as horse sense quantitated. It will, if judiciously used, keep the overenthusiastic researcher from drawing unjustified conclusions and enable the overcautious investigator to express with confidence the full meaning of his findings. All this can and should be achieved with due consideration of the confusion that results to the reader if a writer adorns his treatise with countless standard deviations, chi squares, T-tests and other statistical symbols.

Few physicians have the time, and perhaps not a great many have the ability, to become master statisticians. Trained statisticians are available

for the solving of complicated statistical problems, but their readiness to give aid does not relieve the clinical investigator of the need to familiarize himself with the basic principles and general application of the statistical method. A brief and admirably lucid book, written specifically for those who require no more than this, is that by Hill.* Heretofore, many clinical investigators have handicapped themselves by failing to familiarize themselves with works such as this, and the current trend toward routine, appropriate statistical analysis of clinical research data is a constructive, and probably an overdue, development.

ARMY MEDICAL TRAINING PROGRAM

THE Army Medical Corps has extended to November 1 its time limit for medical-school graduates to apply for commissions under the Civilian Resident and Intern Training Program. This opportunity must impress itself upon all recent graduates in view of the increased need for medical personnel to care for the nation's expanding forces, and the obvious intention of the authorities to fill the need.

Under the program, according to a recent release from the Office of the Surgeon General, selected individuals serve out their internships and residencies in civilian hospitals of their choice — interns as first lieutenants of the Medical Reserve Corps and residents with the same rank in the Regular Army Medical Corps. Both receive full pay and allowances of their rank with $100 a month in addition as a professional volunteer bonus.

Upon completion of a year's training interns must apply for Regular Army commissions and may qualify for resident training. Residents, upon concurrence of the hospital, may continue their training with a view to qualifying for specialty courses leading to certification by American Specialty Boards. The Graduate Training Program may here continue as the Career Management Program under which medical officers are assured of continuation in their specialties during Army service, except in the case of administrative or staff careers. Participating officers are expected to serve a year of active duty for each year of training they receive.

*Hill, B. *Principles of Medical Statistics.* Second edition. 185 pp. London: The Lancet Ltd., 1939.

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KELLER, MAURICE JOSEPH, 412 Jefferson Avenue, Salem.
Columbia University College of Physicians and Surgeons, 1940.

KOHN, FRANCIS JOHN, 13 Pickman Road, Salem.
Middlesex University School of Medicine, 1935. Sponsor: Walter G. Phippen, 31 Chestnut Street, Salem.

KUNIAN, LOUIS, 11 Holly Street, Salem.
Middlesex University School of Medicine, 1942. Sponsor: Richard Thompson, 26 Chestnut Street, Salem.

MacDONALD, ALEXANDER STERLING, JR., 810 Hale Street, Beverly Farms.
Cornell University School of Medicine, 1941.

MARMER, GEORGE, 66 Lewis Street, Lynn.
Middlesex University School of Medicine, 1941. Sponsor: Solomon E. Steiman, 23 Broad Street, Lynn.

MILLS, HERBERT FRANCIS, 257 Broadway, Lynn.
College of Physicians and Surgeons, Boston, 1941. Sponsor: John W. Trask, 90 Ocean Street, Lynn.

MUSMAN, SAMUEL, 274 Western Avenue, Lynn.
Middlesex University School of Medicine, 1934. Sponsor: Samuel Levine, 40 Baltimore Street, Lynn.

ORRIS, HARRY WILLIAM, 244 Ocean Street, Lynn.
Wayne University Medical College, 1942.

PARKER, SYDNEY SANFORD, 10 Poplar Street, Gloucester.
Middlesex University School of Medicine, 1941. Sponsor: William Irving, 35 Middle Street, Gloucester.

SEGAL, ALLAN LOUIS, 8 Naples Road, Salem.
Queen's University School of Medicine, 1938.

SHUB, ALBERT WAYNE, 421 Broadway, Lynn.
Middlesex University School of Medicine, 1943. Sponsor: Leo Maletz, 80 Nahant Street, Lynn.

Henry D. Stebbins, *Secretary*
342 Essex Street, Salem

FRANKLIN

BENNETT, JOHN WESLEY, Northfield.
Temple University School of Medicine, 1940.

NIECKOSKI, JULIAN, 26 Solon Street, Greenfield.
Harvard Medical School, 1941.

Milton M. Sisson, *Secretary*
31 Federal Street, Greenfield

HAMPDEN

BAKER, WALLACE J., 741 Chicopee Street, Willimansett.
Middlesex University School of Medicine, 1942. Sponsor: Stephen A. Mahoney, 378 High Street, Holyoke.

CORCORAN, GEORGE BARTLETT, JR., 84 Park Street, West Springfield.
Yale University School of Medicine, 1944.

FRIED, MARCUS BERNARD, 4 Rittenhouse Terrace, Springfield.
Kansas City University of Physicians and Surgeons, 1933. Sponsor: Alfred Glickman, 95 State Street, Springfield.

GOLD, SOL MARTIN, 15 Greenwood Avenue, Holyoke.
Middlesex University School of Medicine, 1943. Sponsor: Edward P. Bagg, 207 Elm Street, Holyoke.

GOODHUE, FREDERICK WELLS, Westfield State Sanatorium, Westfield.
Tufts College Medical School, 1941.

GREWAL, JOGINDAR SINGH, Westfield State Sanatorium, Westfield.
Boston University School of Medicine, 1926.

JAGODA, LEONARD S., 712 Parker Street, East Longmeadow.
Creighton University School of Medicine, 1935.

KLIBANOFF, SAMUEL, 52 Colfax Street, Springfield.
Harvard Medical School, 1941.

McMILLAN, ALBERT SLOCOMB, 69 North Alhambra Circle, Agawam.
University of Virginia School of Medicine, 1943.

STONE, SAMUEL MONTAGUE, 58 Manor Road, Springfield.
Middlesex University School of Medicine, 1934. Sponsor: George L. Steele, 20 Maple Street, Springfield.

TEITEL, MILTON HENRY, 115 Sumner Avenue, Springfield.
College of Physicians and Surgeons, Boston, 1936. Sponsor: James L. Smead, 26 Temple Street, Springfield.

VASH, GEORGE, 412 Webster Street, New Orleans, La.
University of Vienna, School of Medicine, 1937. Sponsor: Archibald J. Douglas, Westfield.

YETWIN, I. JACQUES, 84 Mayfair Avenue, Springfield.
Middlesex University School of Medicine, 1940. Sponsor: Frederick S. Hopkins, 146 Chestnut Street, Springfield.

Walter W. Williams, *Secretary*
20 Magnolia Terrace, Springfield

HAMPSHIRE

EDELSTEIN, JOSEPH MELVIN, 44 North Elm Street, Northampton.
Tufts College Medical School, 1943.

KOHN, KURT HEINZ, 300 Main Street, Easthampton.
State Medical School of Vinnitza, 1937. Sponsor: Edward D. Williams, 1 High Street, Easthampton.

F. Mary P. Snook, *Secretary*
Worthington

Middlesex East

HALEY, WARREN DRAPER, 14 Oxford Street, Winchester.
Harvard Medical School, 1945.

HICKEY, WILLIAM FRANCIS, JR., 5 Edgehill Road, Winchester.
Harvard Medical School, 1940.

SCHWARTZ, HARRY, 20 Yale Avenue, Wakefield.
Middlesex University School of Medicine, 1942. Sponsor: Howard A. Bouvé, 22 Yale Avenue, Wakefield.

Roy W. Layton, *Secretary*
8 Porter Street, Melrose

Middlesex North

HOLTZMAN, SAUL CHARLES, 10 Carlisle Road, Bedford.
Boston University School of Medicine, 1943.

KAHN, WALTER, 68 Littleton Road, Chelmsford.
University of Bonn School of Medicine, 1921. Sponsor: Philip G. Berman, 174 Central Street, Lowell.

SOUTHWICK, EDWARD HENRY, 169 Fairmount Street, Lowell.
Albany Medical College, 1941.

Brendan D. Leahey, *Secretary*
9 Central Street, Lowell

Middlesex South

ANNUNZIATA, JOSEPH FERDINAND, Main Street, Hopkinton.
Midwest Medical College, 1938. Sponsor: John K. Ruggles, Jr., Hayden Rowe Street, Hopkinton.

AUDIN, FRANCIS J., 114 Danehill Road, Newton Highlands.
University of Buffalo School of Medicine, 1941.

BANDLER, BERNARD, 157 Brattle Street, Cambridge.
Columbia University College of Physicians and Surgeons, 1938.

BOYLE, JEREMIAH JOSEPH, 1737 Cambridge Street, Cambridge.
Tufts College Medical School, 1943.

BROWN, BRUCE ROW, Lane's End, Singletary Lane, Framingham Centre.
Tufts College Medical School, 1943.

CAVALIERI, DOMINIC, 92 Thurston Street, Somerville.
Middlesex University School of Medicine, 1938. Sponsor: Angelo J. Capone, 390A Broadway, Somerville.

CENTNER, PAUL JOSEPH, 21 Greystone Road, Malden.
University of Cincinnati College of Medicine, 1943.

COREY, DAVID ROY, 4 Shawmut Avenue, Cochituate.
Middlesex University School of Medicine, 1939. Sponsor: Arthur E. Taddeo, 75 West Central Street, Natick.

CORRIGAN, SYLVESTER EDWARD, 751 Main Street, Waltham.
Harvard Medical School, 1928.

CROSBY, ROY CAMPBELL, 290 Prospect Street, Framingham.
Tufts College Medical School, 1944.

DELUCA, MARIE A., 319 Union Avenue, Framingham.
Kansas City University of Physicians and Surgeons, 1929. Sponsor: Joseph C. Merriam, 198 Union Avenue, Framingham.

DENICOLAIS, EDWARD J., 255 Hollis Street, Framingham.
Middlesex University School of Medicine, 1942. Sponsor: Joseph C. Merriam, 198 Union Avenue, Framingham.

FEINGOLD, MYER, 584 Salem Street, Malden.
Middlesex University School of Medicine, 1937. Sponsor: Daniel J. Duggan, 3 Hawthorne Street, Malden.

FIORENTINO, DOMENIC SAVERIO, 79 East Main Street, Marlboro.
Middlesex University School of Medicine, 1943. Sponsor: William D. Roche, 196 Main Street, Marlboro.

FISHER, RUSSELL SYLVESTER, 60 Hatfield Road, West Newton.
Medical College of Virginia, 1942.

GOULD, HENRY, 15 West Central Street, Natick.
Kansas City University of Physicians and Surgeons, 1942. Sponsor: Arthur E. Taddeo, 75 West Central Street, Natick.

HARMON, SIDNEY HYMAN, 71 Magazine Street, Cambridge.
College of Physicians and Surgeons, Boston, 1943. Sponsor: William C. Archibald, 837 Massachusetts Avenue, Cambridge.

HURLEY, MELVIN TIMOTHY, 24 Longmeadow Road, Newton Centre.
Stanford University School of Medicine, 1942.

JACOBS, ELI I., 219 Belmont Street, Belmont.
Middlesex University School of Medicine, 1943. Sponsor: James H. Townsend, Mt. Auburn Hospital, Cambridge.

KANTER, STANLEY SAMUEL, 18 Merrigan Street, Arlington.
Washington University School of Medicine, 1943.

KERR, RICHARD CARPENTER, 30 Washburn Street, Newton.
Harvard Medical School, 1943.

LITTER, JULIUS, 106 Strathmore Road, Brighton.
Boston University School of Medicine, 1940.

MACMILLAN, ROBERT JOHNSON, 25 Maple Avenue, Newton
University of Cincinnati College of Medicine, 1943.

MILES, HENRY H. W., 240 Bellevue Street, Newton.
Tulane University School of Medicine, 1939.

MILLER, PAUL RALPH, 89 Parker Avenue, Newton.
Boston University School of Medicine, 1945.

NEWMAN, ARTHUR SAMUEL, 41 Pearl Street, Newton.
Middlesex University School of Medicine, 1943. Sponsor: Charles N. Gettes, 481 Beacon Street, Boston.

O'BRIEN, FREDERICK FRANCIS, 2307 Massachusetts Avenue, Cambridge.
Tufts College Medical School, 1939.

O'KEEFFE, ARTHUR FRANCIS, 24 Oldham Road, West Newton.
Duke University School of Medicine, 1943.

OSTROGER, JOSEPH GEORGE, 203 Middlesex Avenue, Medford.
Middlesex University School of Medicine, 1942. Sponsor: Arthur D. Guthrie, 408 Salem Street, Medford.

REGAN, ELLEN FRANCES, 625 Winter Street, Framingham.
Yale University School of Medicine, 1943.

ROSENMAN, LEONARD DANIEL, 12 Lantern Lane, Newton Centre.
University of Michigan Medical School, 1942.

SCARINGI, JOSEPH, 165 Powder House Boulevard, West Somerville.
Middlesex University School of Medicine, 1937. Sponsor: Walter Jellis, 71 College Avenue, West Somerville.

SHIPP, FRANK LOUDON, 122 Pine Grove Avenue, Newton Lower Falls.
University of Toronto, 1935.

SHUSHAN, ARTHUR A., 316 Belmont Street, Watertown.
Kansas City University of Physicians and Surgeons, 1932. Sponsor: David Rose, 483 Beacon Street, Boston.

TALBOT, HERBERT SELIAN, 104 Pond Street, Natick.
Columbia University College of Physicians and Surgeons, 1928.

WEINBERGER, MAXIMILIAN, Walter Fernald School, Waverley.
University of Vienna, School of Medicine, 1913. Sponsor: Malcolm J. Farrell, Walter Fernald School, Waverley.

WESSLER, STANFORD, 38 Dwhinda Road, Waban.
New York University College of Medicine, 1942.

WILLIAMSON, CHARLES READY, 95 Allen Avenue, Waban.
Harvard Medical School, 1942.

WINSTON, MURRAY RICHARD, 75 Outlook Drive, Lexington.
University of Lausanne School of Medicine, 1939. Sponsor: Norman Wilson, 1101 Beacon Street, Brookline.

WITTENBORG, MARTIN HERMAN, Wayside Inn Road, Framingham.
Johns Hopkins University School of Medicine, 1939.

Alexander A. Levi, *Secretary*
481 Beacon Street, Boston

Norfolk

BARNUM, FRANCIS G., JR., 1776 Beacon Street, Brookline.
Harvard Medical School, 1944.

BIXON, ALVIN MYRON, 220 Mason Terrace, Brookline.
Tufts College Medical School, 1947.

BLACK, MELVIN BERTROM, 16 Parkway Road, Brookline.
Harvard Medical School, 1943.

BONNER, JOSEPH NORBERT, 209 Gerry Road, Chestnut Hill.
Georgetown University School of Medicine, 1942.

COHEN, NATHANIEL MAURICE, JR., 77 Colchester Street, Brookline.
Harvard Medical School, 1946.

COLPOYS, WILLIAM PATRICK, 106 Melville Avenue, Dorchester.
Boston University School of Medicine, 1940.

CONVERSE, J. GERARD, 1152 Brook Road, Milton.
Tufts College Medical School, 1943.

DUB, LEO, 35 Park Street, Brookline.
Medical School of the University of Prague, 1914. Sponsor: Joseph H. Pratt, 94 Upland Road, Brookline.

DUNCAN, THOMAS FRANCIS, 54 Barry Street, Dorchester.
Tufts College Medical School, 1943.

ECHLOV, THEODORE GILBERT, 1682 Beacon Street, Brookline.
Middlesex University School of Medicine, 1940. Sponsor: William Dameshek, 192 Beacon Street, Boston.

EYRE, JOHN DUNHAM, JR., 117 Sherman Road, Chestnut Hill.
Columbia University College of Physicians and Surgeons, New York, 1940.

FINNERTY, EDMUND FRANCIS, JR., 640 Newton Street, Brookline.
Tufts College Medical School, 1943.

GOLDBERG, JACK JACOB, 1614 Beacon Street, Brookline.
College of Physicians & Surgeons, Boston, 1942. Sponsor: Harry Blotner, 419 Commonwealth Avenue, Boston.

GUTMAN, MURRAY, 62 Washington Street, Wellesley.
Chicago Medical School, 1943. Sponsor: Dr. Allen Locke, 76 Washington Street, Wellesley.

HICKS, SAMUEL PENDLETON, 98 Sherman Road, Chestnut Hill.
University of Pennsylvania School of Medicine, 1940.

HILL, ROBERT CLAYTON, 24 Stockwell Street, Roxbury.
Hahnemann Medical College of Philadelphia, 1942.

JONES, WILLIAM NORMAN, 9 Chestnut Street, Boston.
University of Chicago, The School of Medicine, 1940.

KAUFMAN, ALAN L., 65 Green Street, Brookline.
Middlesex University School of Medicine, 1942. Sponsor: Eli Friedman, 416 Marlboro Street, Boston.

KAYE, MAXWELL ELIAS, 86 Neponset Street, Canton.
Midwest Medical College, 1938. Sponsor: Valmore A. Pelletier, 38 Cottage Street, Norwood.

KNEISEL, JOHN JUNIOR, 2 Netherlands Road, Brookline.
Harvard Medical School, 1938.

KVITKA, LAWRENCE, 39 Arlington Road, Brookline.
Middlesex University School of Medicine, 1943. Sponsor: Henry Baker, 4 Greenway Street, Brookline.

MANN, BERNARD FREEMAN, JR., 34 Highview Street, Westwood.
Boston University School of Medicine, 1940.

MURRAY, JOSEPH E., 316 St. Paul Street, Brookline.
Harvard Medical School, 1943.

QUINN, EDWARD JAMES, 87 St. Mary's Street, Brookline.
University of Vermont College of Medicine, 1921.

ROGERS, THEODORE, 929 Blue Hill Avenue, Dorchester.
Middlesex University School of Medicine, 1942. Sponsor: Saul M. Marcus, 520 Beacon Street, Boston.

SOLOW, ALFRED LEONARD, 62 South Main Street, Sharon.
Middlesex University School of Medicine, 1943. Sponsor: William Bourke, Union Street, Walpole.

STAHLER, SIDNEY, 106 E. Foxboro Street, Sharon.
New York Medical College, Flower and Fifth Avenue Hospital, 1942.

STANLEY, MALCOLM MCCLAIN, 37 Garrison Road, Brookline.
University of Louisville School of Medicine, 1941.

STERLING, HASKELL, 389 Harvard Street, Brookline.
Middlesex University School of Medicine, 1943. Sponsor: Hyman Morrison, 483 Beacon Street, Boston.

TRAFTON, MARION ZOTTOLI, 26 Upland Avenue, Dorchester.
Boston University School of Medicine, 1940.

WEISS, JESS BERNARD, 150 Washington Street, Dorchester.
Middlesex University School of Medicine, 1943. Sponsor: David Hurwitz, 520 Beacon Street, Boston.

ZAMBON, LEO UBALDO, 127 Lexington Avenue, Needham.
Middlesex University School of Medicine, 1939. Sponsor: David E. Mann, 863 Great Plain Avenue, Needham.

Basil E. Barton, *Secretary*
10 Richwood Street, W. Roxbury

NORFOLK SOUTH

ENTIN, MOSES JACOB, 37 Woodward Avenue, Quincy.
Middlesex University School of Medicine, 1943. Sponsor: Harry Braverman, 43 School Street, Quincy.

HAGLER, SUMNER, 144 Kingsley Road, Kenberma.
Columbia University College of Physicians and Surgeons, 1943.

KEIGAN, ARCHIE GRAHAM, 276 Quincy Avenue, East Braintree.
Tufts College Medical School, 1944.

KINGSLAND, LAWRENCE CHAPPELL, JR., 19 Howe Street, Hingham.
Harvard Medical School, 1940.

LEMON, HENRY MARTYN, 66 Albatross Road, Quincy.
Harvard Medical School, 1940.

NEVINS, SIMON HARRY, 611 Adams Street, Quincy.
Middlesex University School of Medicine, 1925. Sponsor: James M. Ward, 1186 Hancock Street, Quincy.

RUBIN, FRANK FRED, 795 Southern Artery, Quincy.
Middlesex University School of Medicine, 1936. Sponsor: Frederick N. Manley, 1200 Hancock Street, Quincy.

SLOANE, WILLIAM CHARLES, 15 So. Main Street, Randolph.
Middlesex University School of Medicine, 1933. Sponsor: Robert O. Gilmore, 1159 Hancock Street, Quincy.

SLOMKOWSKI, THADDEUS JOSEPH, 78 Alstead Street, North Quincy.
Boston University School of Medicine, 1943.

WOOD, DWIGHT REYNOLDS, 1070 Main Street, South Weymouth.
Tufts College Medical School, 1943.

Ebenezer K. Jenkins, *Secretary*
Norfolk County Hospital, So. Braintree

PLYMOUTH

CALITRI, JOSEPH FRANCIS, 17 Central Square, West Bridgewater.
College of Physicians and Surgeons, Boston, 1942. Sponsor: George A. Moore, 167 Newbury Street, Brockton.

CARPINELLA, CHARLES JEREMIAH, 94 Moraine Street, Brockton.
Middlesex University School of Medicine, 1931. Sponsor: Michael F. Barrett, 231 Main Street, Brockton.

CORDARO, VINCENT FRANK, Bryant Hotel, Brockton.
College of Physicians and Surgeons, 1941. Sponsor: Michael F. Barrett, 231 Main Street, Brockton.

DAVIS, SAUL PAUL, 16 Cottage Street, Brockton.
Middlesex University School of Medicine, 1943. Sponsor: William Walker, 11 Arlington Street, Brockton.

HASSETT, ARTHUR JOSEPH, JR., 26 Pierce Road, Weymouth.
Tufts College Medical School, 1943.

JACOBS, EDWARD LEE GREGORY, 43 Center Street, North Easton.
Middlesex University School of Medicine, 1942. Sponsor: Fred Weiner, 231 Main Street, Brockton.

KAPLAN, MORRIS, Bridgewater State Hospital, Bridgewater.
College of Physicians and Surgeons, Boston, 1937. Sponsor: John H. Weller, Bridgewater State Hospital, Bridgewater.

OPPENHEIM, HARRY, 239 Howard Street, Rockland.
College of Physicians and Surgeons, Boston, 1937. Sponsor, Ernest E. Wiesner, 129 West Elm Street, Brockton.

THIERY, RAYMOND DONLE, Bridgewater State Hospital, Bridgewater.
Harvard Medical School, 1923.

VALATKA, JOSEPH AUGUST, 335 Washington Street, Abington.
Middlesex University School of Medicine, 1941. Sponsor: John M. Peckham, 131 North Avenue, North Abington.

Samuel Gale, *Secretary*
The Checkerton, Brockton

SUFFOLK

ALLEN, HENRY FREEMAN, 200 Beacon Street, Boston.
Harvard Medical School, 1943.

BONNER, CHARLES DOUGLASS, 2 Lattimore Court, Boston.
Boston University School of Medicine, 1944.

BONNER, FRANCES JONES, 2 Lattimore Court, Boston.
Boston University School of Medicine, 1943.

BONNET, PHILIP DIRLAM, 296 Allston Street, Brookline.
Harvard Medical School, 1936.

BRODIE, SIDNEY, 17 Stearns Road, Brookline.
George Washington University School of Medicine, 1943.

CRANE, CHILTON, 135 Aspinwall Avenue, Brookline.
Harvard Medical School, 1938.

CURTISS, CONSTANCE, Glezen Lane, Wayland.
Western Reserve University School of Medicine, 1945.

FORSHAM, PETER HUGH, 779 Huntington Avenue, Boston.
Harvard Medical School, 1943.

FRANSEEN, ELMER FREDERICK, 45 Hereford Street, Boston.
Harvard Medical School, 1940.

FUNKENSTEIN, DAN HERTZ, 50 Peterborough Street, Boston.
Tulane University School of Medicine, 1934.

GRAY, SEYMOUR JEROME, 282 Warren Street, Brookline.
University of Pennsylvania School of Medicine, 1936.

HEFFERNAN, ELMER WESLEY, 118 Riverway, Boston.
Tufts College Medical School, 1944.

HOWE, CALDERON, 29 Hillcroft Road, Jamaica Plain.
Harvard Medical School, 1942.

JEFFERIES, WILLIAM MCKENDREE, 30 No. Anderson Street, Boston.
University of Virginia Department of Medicine, 1940.

KENWORTHY, ROGER ARTHUR, Carney Hospital, South Boston.
University of Vermont College of Medicine, 1940.

KERHULAS, ANDREW ANTHONY, 108 Henry Street, Cambridge.
Duke University School of Medicine, 1943.

KLIGERMAN, SIDNEY, 469 Commonwealth Avenue, Boston.
University of Illinois College of Medicine, 1939.

LUONGO, MICHAEL ANTHONY, 69 Gladstone Street, East Boston.
Boston University School of Medicine, 1943.

PEARSON, CARL MAXWELL, 750 Harrison Avenue, Boston.
Boston University School of Medicine, 1946.

PETERSON, NORVELL LOUIS, 30 Evans Way, Boston.
Kansas City University of Physicians and Surgeons, 1942.
Sponsor: E. Allan Brown, 75 Bay State Road, Boston.

PROCTOR, WALLACE, 750 Harrison Avenue, Boston.
University of California Medical School, 1933.

RYDER, BROOKS, 49 East Springfield Street, Boston.
Tufts College Medical School, 1944.

SAUNDERS, PETER, 4 Montrose Street, Roxbury.
Hungarian Royal University, 1937. Sponsor: Sidney C. Wiggin, 270 Commonwealth Avenue, Boston.

SCIACCA, GUY FRANCIS, 23 Unity Court, Boston.
Middlesex University School of Medicine, 1939. Sponsor: Salvatore Lima, 281 Hanover Street, Boston.

SINGER, PERETZ, 63 Thomas Park, South Boston.
Middlesex University School of Medicine, 1936. Sponsor: John J. Todd, 587 Beacon Street, Boston.

SPANGLER, ARTHUR STEPHENSON, 154 Riverway, Boston.
Harvard Medical School, 1943.

STANBURY, JOHN BRUTON, 185 Mt. Auburn Street, Cambridge.
Harvard Medical School, 1939.

STIMSON, ALLAN BRADDOCK, 300 Longwood Avenue, Boston.
Harvard Medical School, 1943.

THALER, RICHARD WINSTON, 25 Bennet Street, Boston.
Harvard Medical School, 1945.

WERMER, HENRY, 97 Strathmore Road, Brookline.
University of Vienna, School of Medicine, 1936. Sponsor: Harry C. Solomon, 74 Fenwood Road, Boston.

WEXLER, JACOB, 60 Seaver Street, Roxbury.
Middlesex University School of Medicine, 1933. Sponsor: David B. Stearns, 416 Marlboro Street, Boston.

WILSON, JOHN LONG, 99 Myrtle Street, Boston.
Harvard Medical School, 1939.

Charles G. Shedd, *Secretary*
422 Beacon Street, Boston

WORCESTER

BUTLER, PHILIP SUMNER, 14 North Parkway, Worcester.
Tufts College Medical School, 1943.

CASALE, WALTER, 40 Cedar Street, Worcester.
Long Island College of Medicine, 1936.

CHANDLER, CHARLES FASSETT, Sterling Junction.
Boston University School of Medicine, 1946.

MACGILPIN, HAROLD HARRINGTON, JR., 8 Suburban Road, Worcester.
University of Pennsylvania School of Medicine, 1942.

MALMQUIST, CARL YALE, JR., 4 Coventry Road, Worcester.
Yale University School of Medicine, 1946.

MARTIN, WILLIAM KIRWAN JOSEPH, JR., 74 Commodore Road, Worcester.
New York Medical College, Flower and Fifth Avenue Hospitals, 1937.

MORRISON, JAMES MARTIN, 14 Oberlin Street, Worcester.
St. Louis University School of Medicine, 1944.

PIERCE, JAMES FRANCIS, 11 Charlotte Street, Worcester.
Georgetown University School of Medicine, 1946.

SHANNON, MARY C., 334 Highland Street, Worcester.
Kansas City University of Physicians and Surgeons, 1927.
Sponsor: Smith G. Philips, 36 Pleasant Street, Worcester.

VAMVAS, ANTHONY D., JR., 7 Old Brook Drive, Worcester.
Boston University School of Medicine, 1946.

Donald Hight, *Secretary*
57 Cedar Street, Worcester

WORCESTER NORTH

COBB, SIDNEY, 3901 Eliot Road, Fort Devens.
Harvard Medical School, 1942.

DESCHENES, ALBERT ALPHONSE, 72 Delisle Street, Fitchburg.
Boston University School of Medicine, 1941.

GELINAS, JOSEPH ARMAND, 190 Milk Street, Fitchburg.
Laval University Faculty of Medicine, 1945.

James G. Simmons, *Secretary*
30 Myrtle Avenue, Fitchburg

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1948

RÉSUMÉ

DISEASES	AUGUST 1948	AUGUST 1947	SEVEN-YEAR MEDIAN
Chancroid	4	2	2*
Chicken pox	163	179	123
Diphtheria	18	17	11
Dog bite	1201	1021	1021
Dysentery, bacilary	12	9	14
German measles	47	41	46
Gonorrhea	334	308	374
Granuloma inguinale	0	1	0*
Lymphogranuloma venereum	2	1	0*
Malaria	1	7	13
Measles	595	125	281
Meningitis, meningococcal	6	0	5
Meningitis, Pfeiffer-bacillus	1	1	1
Meningitis, pneumococcal	0	0	0†
Meningitis, staphylococcal	0	1	0†
Meningitis, streptococcal	0	1	0†
Meningitis, other forms	2	1	0†
Meningitis, undetermined	7	2	3†
Mumps	428	170	271
Pneumonia, lobar	76	77	76
Poliomyelitis	69	80	62
Salmonellosis	12	19	22
Scarlet fever	74	72	195
Syphilis	166	187	341
Tuberculosis, pulmonary	285	171	233
Tuberculosis, other forms	15	10	18
Typhoid fever	6	2	5
Undulant fever	2	7	6
Whooping cough	209	475	498

*Four-year median.

†Six-year median.

COMMENT

Diseases with an incidence above the seven-year median included chicken pox, diphtheria, dog bite, measles, mumps and poliomyelitis.

Diseases with an incidence below the seven-year median included salmonellosis, scarlet fever, undulant fever and whooping cough.

A number of cases reported as meningitis, undetermined, poliomyelitis and lymphocytic choriomeningitis had the same clinical and spinal-fluid findings.

Measles had the highest incidence for August since 1916. Mumps had the highest August incidence since it was made reportable. Whooping cough continues to be reported at the lowest level since 1915.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Arlington, 2; Boston 10; Chicopee, 1; Everett, 1; Natick, 2; Revere, 1; Somerville, 1; total, 18.

Dysentery, amebic, was reported from: Newton, 2; total, 2.

Dysentery, bacillary, was reported from: Chelsea, 1; Waltham, 1; Worcester, 10; total, 12.

Lymphocytic choriomeningitis was reported from: Fitchburg, 4; Malden, 1; total, 5.

Malaria was reported from: Cambridge, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 2; Framingham, 1; Holyoke, 1; Springfield, 1; Worcester, 1; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Auburn, 1; total, 1.

Meningitis, other forms, was reported from: Haverhill, 1; Holden, 1; total, 2.

Meningitis, undetermined, was reported from: Brockton, 1; Leominster, 4; Melrose, 1; Worcester, 1; total, 7.

Poliomyelitis was reported from: Abington, 1; Adams, 1; Andover, 1; Ayer, 1; Becket, 1; Boston, 1; Brookline, 2; Carver, 1; Danvers, 2; Dracut, 1; Gloucester, 3; Groveland, 2; Ipswich, 1; Lincoln, 1; Middleboro, 1; New Bedford, 1; Newton, 3; Northampton, 1; Norwood, 1; Peabody, 1; Quincy, 1; Revere, 1; Salem, 3; Springfield, 3; Swampscott, 1; Waltham, 2; Watertown, 2; Wellesley, 1; West Boylston, 17; West Bridgewater, 1; West Stockbridge, 1; Weston, 2; Whitman, 1; Winthrop, 1; Worcester, 5; total, 69.

Salmonellosis was reported from: Lowell, 2; Malden, 1; Methuen, 2; Norfolk, 6; Somerville, 1; total, 12.

Septic sore throat was reported from: Fall River, 1; Rutland, 1; total, 2.

Tetanus was reported from: Lexington 1; Newton, 1; total 2.

Trichinosis was reported from: Fall River, 3; Lawrence, 1; Swansea, 2; Waltham, 1; total, 7.

Typhoid fever was reported from: Beverly, 1; Boston, 1; Gardner, 1; Lowell, 1; New Bedford, 1; Somerset, 1; total, 6.

Undulant fever was reported from: Malden, 1; Warren, 1; total, 2.

BLUE CROSS — BLUE SHIELD

THE BLUE SHIELD DOLLAR

Associated Medical Care Plans, in a recent release, presents an analysis of payments to physicians for benefits provided under the average surgical type of subscriber contract.

Four types of surgical procedure — appendectomies, tonsillectomies and obstetric and gynecologic operations — account for approximately sixty cents of every dollar paid to physicians. The next twenty-five cents goes to pay for approximately seventy surgical procedures. Payments for x-ray and anesthesia are on the increase, owing perhaps to an increasing number of physicians entering these fields.

Female subscribers cost about three times as much for surgical benefits as do male subscribers, with female dependents only slightly less expensive. While these costs are due largely to obstetrics and gynecology, female costs in general surgery are also above the average, principally on account of breast operations.

Male dependents cost more than female dependents. because of herniotomies, circumcisions, fractures and dislocations, boys breaking almost exactly twice as many bones as their sisters do.

CORRESPONDENCE

DEPRIVATION AND RESTORATION OF LICENSES

To the Editor: At the meeting of the Board of Registration in Medicine held September 16, it was voted to revoke the registrations of Dr. Samuel C. Zundell, 332 Blue Hills Parkway, Milton, Massachusetts, and Dr. Alfred J. Leary, 195 Ashmont Street, Dorchester (because of ill health), and to restore the registration of Dr. David Ginsburg, 505 Armory Street, Springfield, Massachusetts.

George L. Schadt, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEW

Heart: A physiologic and clinical study of cardio-vascular diseases. By Aldo A. Luisada, M.D. With a foreword by Herrman L. Blumgart, M.D. 4°, cloth, 653 pp., with 352 illustrations. Baltimore: The Williams and Wilkins Company, 1948. $10.00.

The disrupting effects of two world wars upon European medicine have accelerated the development of the United States as the international center of medical science. The turbulence of the political situation led in the past twenty years to the emigration of many outstanding foreign physicians. Dr. Luisada brought to this country some years ago the knowledge of the Italian school of medicine. It is to the benefit of American physicians that books by foreign investigators be available in English, since Americans are notoriously unwilling, or unable, to utilize material in other languages.

This book is an attempt to cover the field of cardiovascular diseases, a task, as Dr. Blumgart says in the foreword, that is "herculean." There are thirty-three chapters followed by a section on diets, and one on prescriptions, and inserted at the end there is a folded table of "summary of treatment in cardiovascular emergencies."

There are as many schemes of classification of cardiovascular diseases as there are authors — this one avoids the etiologic, except when correlated with the fundamental anatomicoclinical syndromes on which the classification is based. The historical data and extensive bibliography make the book valuable as a reference, particularly in its use of eponyms, many of which, though unfamiliar, may help in establishing priority in description of certain syndromes.

The physiologic approach to cardiovascular problems has advantages, and the schematic illustrations and descriptions of experiments with models should be useful to students.

Anatomy is well covered with many figures. The chapter on "Normal Functions" is followed by those on "Clinical Study" and "Technical Study." Newer methods of investigation with radioactive isotopes and cardiac catheterization will undoubtedly make much of the latter chapter of historical interest only, within a few years, and such procedures as diagnostic pneumomediastinum seem already so. The section of phonocardiography is extensive and presents the author's notable experience in this relatively new field, and gives a practical background for those using this technic.

The causes of cardiovascular diseases are considered, and this chapter precedes the descriptions of rheumatic disease, endocardial diseases, valvular defects of the left and right sides of the heart, simple shunts and complex malformations.

The disturbances of rate and rhythm of the heart are illustrated with diagrams, electrocardiograms and phonocardiograms and the clinical descriptions, tests, diagnosis and treatment combined with these objective records.

Diseases of the myocardium, metabolic and endocrine diseases and coronary-artery diseases are given separate chapters. Although it is obvious that detailed consideration of these conditions cannot be given in a single volume covering all cardiovascular disease, it is commendable that so much of the literature has been noted and so many procedures mentioned that can be studied in the original references.

Pericardial diseases are given twenty-seven pages, and diseases of the aorta twenty-six, whereas hypertension is covered in twelve pages. This reflects the special interests and investigations of the author, as noted in his preface. In the treatment of hypertension sodium restriction is referred to only by the statement that a "reduction of salt may be indicated." The rice diet is not mentioned. Surgical treatment is allotted less than half a page.

The final chapters cover cor pulmonale, hypotension, diseases of the arteries and veins, borderline syndromes, complex heart diseases, paroxysmal dyspnea, heart failure, the cardiac patient as an obstetric and surgical risk, drugs, the management of the cardiac patient and medical treatment of common cardiac conditions.

The book is well printed on high-grade paper in the two column to a page method that has become popular. It is so designed as to be useful to medical students, practitioners, cardiovascular specialists and reference libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgical Applied Anatomy. By Sir Frederick Treves, Bart. Eleventh edition, revised by Lambert Rogers, M.Sc., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., professor of surgery, University of Wales, and member of the Court of Examiners, Royal College of Surgeons of England. 12°, cloth, 560 pp., with 192 illustrations, including 66 in color. Philadelphia: Lea and Febiger, 1947. $6.00.

This manual has enjoyed a long and honorable career. It first appeared in 1883, and after the death of Sir Frederick Treves was continued in succession by Sir Arthur Keith, Professor C. C. Choyce and Professor Rogers. Despite limitations of time the present edition has been revised radically. Composed and printed in Great Britain and bound in the United States, the book is well published. It was originally intended for students of surgery as a manual of applied anatomy. It should prove of value to surgeons as a quick reference source.

The Yearbook of Psychoanalysis. Volume 3, 1947. Managing editor, Sandor Loran, M.D. 8°, cloth, 309 pp. New York: International Universities Press, 1948. $7.50.

In this serial volume are brought together for convenient reference twenty papers, originally published in a number of different periodicals. The paper of A. Garma on psychoanalytic investigations in melancholias and other types of depressions was published originally in Italian but has been translated into English for this publication. The volume is well published and should be in all large medical libraries and in psychiatric collections.

Man. Weather. Sun. By William F. Petersen, M.D. 8°, cloth, 462 pp., with 294 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $10.00.

Dr. Petersen presents a detailed study of man in relation to the air mass in which he lives. The author summarizes the work upon the subject during the decades 1920-1930 and 1930-1940. The studies of the first decade demonstrated that the weather was an important factor in the life of man, but that progress was retarded because of the lack of encouragement from medical and scientific circles. In the second decade progress was advanced, and observations were made relating to the reaction of the normal and the sick person to weather changes. Dr. Petersen summarizes the results as follows: conditioning by the weather, whether the subject is exposed directly or sheltered in the home or hospital; the reflection of the weather in the precipitation of diverse clinical pictures; the conditioning of genetic trends during the earliest stages of development; the conditioning of the mental reaction of the normal, and of the abnormal reaction in the psychopathic person; and the obvious reflection of the weather in births and deaths in the population at large. In 1940 the exceptional opportunity of studying daily a set of adult triplets over a period of six weeks was presented to the author, and the results of these comprehensive studies demonstrated that genetically like persons react similarly to the meteorologic environment in which they exist. Previously studies were made on isolated persons. Of importance in these studies of the triplets was the demonstration of the magnitude of the biochemical and biophysical reactions. The book is divided into five parts: the first, comprising one hundred and twenty-one pages, gives in detail the observations on the triplets; the second describes the reaction of the population in births, deaths, suicides, twinning and psychopathic admissions, based on the results of the triplet observations; the third considers man as a cosmic resonator and discusses cosmic, weather and organic rhythms, organic cycles, blood reaction, vital indexes of scarlet fever, epilepsy and death, and the trends of 1930 to 1943 applied to longer rhythms than one year; the fourth, entitled "The symphony of sun and man," considers the possible integration of human reactions and solar rhythm of long range, including the discussion of the sun and the sunspot cycle, epidemics, death, blood reaction, modification of genetic trends of conceptions, weight and length ratio of the newborn and twinning, and genius; the fifth, "The great year," is a study of the Egyptian period from 5400 B.C. to 1240 A.D., which develops the probability of long-range trends in cultures and civilizations, and their significance for the present and the future. Appended to the text are detailed individual charts of the observations on the triplets. Indexes of authors, subjects and illustrations conclude the volume. Some of the part headings are fanciful and not indicative of the contents of the chapters. There is a large amount of statistical material, including charts and curves throughout the text. The publisher has solved a difficult matter in makeup and has produced a well published volume. The book should be in all public-health collections.

Psychosomatic Medicine: A study of the sick society. By James L. Halliday, M.D., D.P.H. 8°, cloth, 277 pp. New York: W. W. Norton & Company, Inc., 1948. $3.50.

This study is based on the application of psychosomatic medicine to the illnesses of communities and social groups. The author puts forward the thesis that groups may become physically ill and become sick populations, characterized by high morbidity and mortality rates, owing to mass malnutrition, infectious diseases, infestations and so forth. Likewise, a group has psychologic or social needs, and if these needs are not satisfied its psychologic or social health declines and the group becomes a sick society; he calls the medical approach to this sick society psychosocial medicine. The author would have preferred the term "social medicine" but was debarred from its use by the pre-emption of the term by others. The material in the book is largely derived from original researches — clinical, statistical and methodologic — that employed the psychosomatic approach and extended over a period of ten years. The text is divided into three main divisions: medical logic, in which some principles of etiology are discussed; psychosomatic medicine, subdivided into four chapters, in which the concept and incidence of psychosomatic affections, psychosomatic medicine and the problems of chronic and recurring illness, and the ontogenetic theory and psychosomatic affections are considered; the sick society, in six chapters, which discusses epidemiology, a declining birth rate and psychologic health, psychosocial medicine, the case of Britain as a sick society, the mining community as a sick society and problems of reintegration, including the social function of medicine and the social functions of politics. In conclusion, the author states that as social sickness is a disease the basic observations upon it are appropriately made in terms of medicine and arranged in familiar medical categories, but that much further field investigation needs to be done, before social therapeutics becomes a subject of medicine in its own right. The text is concluded with an appendix comprising notes on five chapters, including the bodily mechanism of emotion, the significance of a psychosomatic illness, social health and the United States, and the

incidence of psychosomatic affections in underground miners. A good index concludes the volume. The monograph is well published and should be in all public-health collections.

You and Your Doctor: A frank discussion of group medical practice and other modern trends in American medicine. By Benjamin F. Miller, M.D., clinical professor of medicine, George Washington University School of Medicine, and research associate in medicine, National Research Council. 8°, cloth, 183 pp. New York: Whittlesey House, 1948. $2.75.

In this popular book Dr. Miller analyzes the various aspects of medical practice of the present time, including the status of the general practitioner, the diagnostician, group clinics and the modern hospital. He also discusses freedom from emotional illness, periodic medical checkups, post-mortem examinations, medical education and research, and interstate medical care. On the national level is noted the need of an adequate disaster service preferably operated by a federal agency. Under the heading "Who Should Administer National Medical Care?" Dr. Miller considers impartially the agencies best able to promote and operate a national plan, and although a member of the American Medical Association and favoring it in his analysis, he is convinced that the United States Public Health Service is at present in the best position to operate a plan co-ordinating preventive medicine, curative or clinical medicine and medical research, the three major essentials of such a national plan. If the Public Health Service cannot assume the promotion and operation of a national plan, Dr. Miller suggests that a special federal agency be established for that purpose. The book is well published, except that it lacks an index. The volume should be in all public-health collections.

Textbook of Gynecology. By Emil Novak, M.D., assistant professor of gynecology, Johns Hopkins University School of Medicine, and gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore. Third edition. 8°, cloth, 742 pp., with 484 illustrations. Baltimore: The Williams and Wilkins Company, 1948. $8.00.

Dr. Novak has brought up to date this third edition of his standard textbook on gynecology. A considerable number of illustrations, some in color, have been added. Dr. H. S. Everett has revised his chapter on female urological conditions of special interest to the gynecologist. A list of selected references is appended to each chapter, and there is a good index. The publishing is well done. The book should be in all medical libraries and in the private collections of gynecologists and physicians interested in the subject.

Clinical Toxicology. By Clinton H. Thienes, M.D., Ph.D., professor of pharmacology and head of the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California, Los Angeles, an attending pathologist (toxicology), Los Angeles County Hospital; and Thomas J. Haley, Ph.D. Second edition. 12°, cloth, 373 pp. Philadelphia: Lea and Febiger, 1948. $3.50.

The second edition of this popular manual for students and general practitioners has been thoroughly revised and enlarged to the extent that the text has been entirely reset and printed from new type. Sections have been added on dicoumarol, heparin, thiouracil, DDT, gold, BAL and streptomycin. Material has also been added on proteins, amino acids and vitamins in the treatment and prevention of poisoning. The section on the chemical identification of poisons has been enlarged to include tables, comparing color and other reactions, as well as new tests for arsenic, the barbiturates, cyanide and the sulfonamides. The nomenclature has been brought into line with the thirteenth edition of *United States Pharmacopoeia*, the eighth edition of the *National Formulary* and the 1947 edition of *New and Nonofficial Remedies*. The material is well arranged, and the volume is well published. The manual should prove useful as a reference source to libraries and to all persons interested in the subject.

Organic Form and Related Biological Problems. By Samuel J. Holmes. 8°, cloth, 169 pp. Berkeley: University of California Press, 1948. $5.00.

This small volume practically consists of thirteen separate essays on closely related subjects in biology. The short essay on the regeneration of blood and its bearing on morphogenic theory and the long one on cancer as a biologic problem are of direct medical significance. In the essay on cancer the author presents a comprehensive survey of the current theories on the causation of cancer, with emphasis on genetic factors. Likewise of interest is the article on autocatalytic enzymes and the origin of life. Six of the articles were published previously in scientific periodicals. A bibliography arranged by chapters follows the text, and an index concludes the volume. The text is well written, and although it makes admittedly difficult reading is recommended for all medical libraries and, naturally, for biologic collections. It should be available to all persons interested in carcinogenesis. The book is well published.

NOTICES

ANNOUNCEMENTS

Dr. Jackson M. Thomas announces the opening of an office at 311 Beacon Street, Boston, for the practice of psychiatry.

Dr. James L. Tullis announces the opening of an office at 1101 Beacon Street, Brookline, for the practice of internal medicine and hematology.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The fall, winter and spring meetings of the Massachusetts Medico-Legal Society will be held, respectively, on Wednesday, October 20, 1948, in the Magrath Library, Building E, Harvard Medical School, Boston, on Wednesday, February 9, 1949, in the Magrath Library, Building E, Harvard Medical School, Boston, and on Wednesday, May 25, 1949, in the Worcester Memorial Auditorium, Worcester. The program for the fall meeting at 2:30 p.m. on October 20 is as follows:

Business Meeting.

Air Embolism as a Complication of Abortion. Leroy T. Stokes, M.D., and Richard Ford, M.D.

Acute Isolated Myocarditis. David Dow, M.D., Daniel J. Kiley, M.D., and Michael Luongo, M.D.

Unexpected Death from Beri-beri Heart Disease. Walter W. Jetter, M.D.

Suicidal Gunshot Injury. James H. McCann, M.D., and Russell S. Fisher, M.D.

Collation.

The following amendment to the by-laws, as proposed by the Standing Committee, will be considered:

That Article 1, Paragraph 2, of the by-laws be amended by the addition of the words "or honorary," so as to read as follows: "The Society may, at any stated meeting, elect to associate or honorary membership such persons distinguished in medical, legal or technical science as the Standing Committee, acting as a nominating committee, may recommend."

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at the Murphy General Hospital, Waltham, on Wednesday, October 20.

PROGRAM

11:30 a.m. Business.

12:00 noon. Clinical papers. "Management of Hyperthyroidism" by Colonel Otto L. Churney, M.C., and Lieutenant Colonel Ralph L. Cox, M.C.

1:00 p.m. Luncheon.

Future meetings will be held on December 6, 1948, at Sanders Theater, Cambridge, on January 26, 1949, at Newton-Wellesley Hospital, and on April 20, 1949 (annual meeting), at the Hotel Continental, Cambridge. The December meeting will consist of a symposium on diabetes and will be a joint meeting with Suffolk, Norfolk and Middlesex South in connection with National Diabetes Week.

(*Notices concluded on page xiii*)